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ETIOLOGY OF GALLSTONES

A CRITICAL SURVEY OF THE LITERATURE AND A STUDY OF THE APPLICABILITY OF VARIOUS THEORIES IN TWO HUNDRED AND THIRTY-NINE OPERATIVE CASES

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Study as to the cause of gallstones has been extensive since they were first reported, in the fourteenth or the fifteenth century. Early thought was purely speculative, but since the time of Naunyn a mass of clinical and experimental data has been accumulated. A multitude of theories have been propounded, none of which is adequate to explain the whole problem.

A fundamental difficulty has been the failure to recognize that the conditions which determine the formation of biliary calculi are multiple and complex. In addition, there are several varieties of gallstones. According to the classification of Naunyn there are pure cholesterol stones, calcium bilirubinate stones, and the common "mixed" gallstones. Each of these may be determined by the combination of a different set of circumstances. In the series of observations we shall discuss, only the pure cholesterol stone and the common "mixed" gallstone will be considered.

The cause of gallstones must be sought among many factors. These factors resolve themselves generally into two groups: The first is related to changes in the composition of the hepatic bile, whether due to aberrations in the general metabolism (hypercholesteremia, diet, systemic disease or pregnancy) or to disease or injury of the liver; the second group is related to changes taking place directly in the gallbladder or bile ducts and favoring the formation of calculi.

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The metabolic theory, which assumes that disturbances in metabolism so change the hepatic bile as to predispose to the formation of concrements, has been brought forward to explain the formation of pure cholesterol stones. It is equally applicable, however, to explain the formation of pigment stones. Giffin,[1] in particular, has emphasized the frequency of gallstones (58 per cent) in adults with congenital hemolytic jaundice. These stones characteristically are hard brown or black pigment stones consisting of bilirubin and calcium bilirubinate. They are apparently related to the pleocholia, or excessive excretion of bile pigment, associated with this condition. Greene and Snell[2] found experimentally that an augmented rate of excretion of pigment in the bile is brought about primarily by an increase in concentration rather than by an increase in the volume of the bile. Pleocholia, therefore, may well predispose to the deposition of this particular form of calculus.

The metabolic theory is usually restricted to the formation of cholesterol stones. As advocated by Chauffard and his co-workers,[3] it assumed a correlation between the concentration of cholesterol in the blood and that in the bile and so maintained that an elevated value for blood cholesterol is a predisposing factor in the formation of gallstones. The clinical experience of Chauffard, Moynihan,[4] Hansen,[5] Dewey[6] and others seemingly has substantiated this belief. The observation of an increased concentration of cholesterol in both the blood and the bile during pregnancy, the frequent onset of clinical symptoms during or immediately after pregnancy and the higher incidence of gallstones in women than in men have all been factors in the acceptance of this theory. Dietary experiments with animals, with the use of diets rich in cholesterol, have demonstrated that the cholesterol content of the blood can be increased markedly by each feeding. This finding has received added confirmation by the work of Wilensky[7] and of Roths-

1. Giffin, H. Z.: Hemolytic Jaundice: A Review of Seventeen Cases, Surg., Gynec. & Obst. **25**:152 (Aug.) 1917.

2. Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile: II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile and Its Constituents, J. Biol. Chem. **78**:691 (Aug.) 1928.

3. Chauffard, A.: Role of Hypercholesterolemia in Pathogenesis of Gall Stones, J. méd. franç. **26**:251 (Aug.) 1927. Chauffard, A.; Laroche, G., and Grigaut, A.: Le tux de la cholésterinémie chez les hépatiques, Compt. rend. Soc. de biol. **70**:20, 1911.

4. Moynihan, B.: Some Aspects of Cholelithiasis, Brit. M. J. **1**:393 (Feb. 28) 1925.

5. Hansen, S.: Die Bedeutung des Cholesterins für die Bildung von Gallensteinen durch experimentelle Untersuchungen beleuchtet, Acta chir. Scandinav. **62**: 483, 1927.

6. Dewey, K.: Experimental Hypercholesterolemia, Arch. Int. Med. **17**:757 (June) 1916.

7. Wilensky, A. O.: Hypercholesteremia, Surg., Gynec. & Obst. **38**:163 (Feb.) 1924.

child and Wilensky.[8] Walsh,[9] Walsh and Ivy [10] and Andrews, Hrdina and Dostal [11] Riegel, Ravdin and Rose,[12] Patey [13] and many others, however, were unable to find such a definite relation between the cholesterol content of the blood and that of either hepatic or gallbladder bile, either in patients or in experimental animals. They therefore concluded that there is no direct relation between the cholesterol content of the blood and the formation of gallstones.

The bile salts in hepatic bile are the specific secretion of the liver cells, and numerous investigators, such as Stadelmann,[14] Whipple,[15] Ivy,[16] Doubilet,[17] Greene, Walters and Frederickson,[18] have shown that this excretion in the bile is an extremely sensitive index of the functional activity of the hepatic parenchyma. The bile salts also have a role in keeping the cholesterol of the bile in solution. Changes in the functional activity of the liver from hepatitis, suppression of secretion or metabolic disturbances may so change the concentration of bile salts in the hepatic bile as to favor the precipitation of cholesterol. The importance of this bile salt–cholesterol ratio in the formation of gallstones will be discussed later in this paper. Excretion of bacteria, bile thrombi or abnormal toxic products due to hepatic damage and other organic changes in the liver and its secretion have been suggested

8. Rothschild, M. A., and Wilensky, A. O.: Studies in Cholelithiasis: I. The Disturbances of the Cholesterin Metabolism as a Factor in Gall Stone Formation, Am. J. M. Sc. **156**:139 (Aug.) 1918; II. The Clinical Relationships of Cholesterinemia to the Pathological Process, ibid. **156**:404 (Sept.) 1918.

9. Walsh, E. L.: The Etiology of Gall Bladder Calculi, Arch. Path. **15**: 698 (May) 1933.

10. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gall Stones, Ann. Int. Med. **4**:134 (Aug.) 1930.

11. Andrews, E.; Hrdina, L., and Dostal, E.: Etiology of Gall Stones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

12. Riegel, C.; Ravdin, I. S., and Rose, H.: Studies of Gall Bladder Function: XV. Cholesterol in Human Liver Bile, J. Clin. Investigation **16**:67 (Jan.) 1937.

13. Patey, D. H.: Modern Views on Mechanism of Formation of Gall Stones, Brit. M. J. **1**:866 (May 20) 1933.

14. Stadelmann, E.: Der Icterus und seine verschiedenen Formen, Stuttgart, Ferdinand Enke, 1891.

15. Whipple, G. H.: Origin and Significance of Constituents of the Bile, Physiol. Rev. **2**:440 (July) 1922.

16. Ivy, A. C.: Factors Concerned in the Evacuation of the Gall Bladder. Medicine **11**:345 (Sept.) 1932.

17. Doubilet, H.: Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administrations, Proc. Soc. Exper. Biol. & Med. **36**:50 (Feb.) 1937.

18. Greene, C. H.; Walters, W., and Fredrickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, J. Clin. Investigation **9**: 295 (Oct.) 1930.

repeatedly as forming the nuclei for stones. Crile [19] concluded that energy changes in the body, affecting the liver and causing abnormality of the bile, result in the formation of stones and that these in turn cause the infection frequently seen in calculous gallbladders. He stated: "Our thesis is that the chemical and physical basis of gallstones is laid by changes in the secretion of the biologically active liver cells and not by changes in the sac that holds and concentrates the bile and performs no other function."

By means of ingenious experiments in which the common duct was catheterized under completely aseptic conditions, Rous, McMaster and Drury [20] have shown the formation of stones without any evidence of stasis, infection or changes in the composition of the blood. They concluded from this experimental work that stones may form from altered hepatic secretion. Rovsing [21] came to a similar conclusion.

Attempts to show a relation between the intake of fluids and the volume of bile secreted by the liver have been unsuccessful. Of seemingly greater significance is the recognized importance of the changes occurring in bile during its passage through the bile ducts and gallbladder. It is here that the controversy concerning the physiologic action of the gallbladder becomes of major importance in evaluating theories concerning the formation of gallstones. The question is: Does the normal gallbladder absorb cholesterol, as has been maintained by Policard,[22] Whitaker,[23] Mentzer,[24] Boyd,[25] Halpert,[26] Sweet [27] and others; does it secrete cholesterol, as has been contended by Elman

19. Crile, G.: Energy Background of Genesis of Gall Stones and of Prevention of Immediate Post-Operative Shock and of Later Digestive Disturbances, Surg., Gynec. & Obst. **60**:818 (April) 1935.

20. Rous, P.; McMaster, P. D., and Drury, D. R.: Observations on Some Causes of Gall Stone Formation: I. Experimental Cholelithiasis in the Absence of Stasis, Infection and Gall Bladder Influences, J. Exper. Med. **39**:77 (Jan.) 1924. Rous, P.; Drury, D. R., and McMaster, P. D.: II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, ibid. **39**:97 (Jan.) 1924.

21. Rovsing, T.: Gall Stones Cause, Not Result, of Infection, Acta chir. Scandinav. **56**:103, 1923.

22. Policard, A.: Sur quelques données histo-physiologiques concernant le mecanisme functionnel et pathologique et de la vésicule et des voies biliaires, Lyon chir. **19**:799, 1922.

23. Whitaker, L. R.: The Relation of Biliary Dysfunction to Lithiasis, New York State J. Med. **34**:221 (March 15) 1934.

24. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, Arch. Surg. **14**:14 (Jan.) 1927.

25. Boyd, W.: Studies in Gall-Bladder Pathology, Brit. J. Surg. **10**:337 (Jan.) 1923.

26. Halpert, B.: The Gall Bladder in the Light of Recent Investigation, Arch. Surg. **19**:1037 (Dec.) 1929.

27. Sweet, J. E.: The Formation of Gall Stones, Am. J. Surg. **40**:162 (April) 1938.

and Graham [28] and originally by Naunyn,[29] or does it normally only concentrate cholesterol, as the observations and experimental data of Ravdin and Johnston,[30] Walsh [9] and Andrews, Schoenheimer and Hrdina [31] indicate? Lichtwitz,[32] in 1914, further complicated the question by suggesting that saturation of the plicae of the gallbladder with cholesterol (by absorption from the bile) and their subsequent dehiscence form the nuclei for "metabolic" stones. Though this theory has been supported recently by Gosset, Bertrand and Loewy,[33] it has been denied by Illingworth [34] and Mackey.[35]

It is generally agreed that the gallbladder extracts water as well as sodium chloride and other inorganic salts from the hepatic bile, concentrating it from seven to ten times (Ravdin and Johnston [30] and others). It would appear from clinical and experimental studies that while the mucosa of the gallbladder may absorb bile salts or cholesterol from the bile this does not occur under normal circumstances. In the presence of an inflammation, when the mucosa is edematous, Dostal and Andrews [36] have shown that bile salts are rapidly absorbed by the wall of the gallbladder. Clinically this is seen most readily in cases of hydrops of the gallbladder. Another explanation is that advanced by Rous, McMaster and Drury [20] in the replacement of the bile (including cholesterol and bile salts) by mucus, which is a specific response of the mucosa of the gallbladder. Aronsohn and Andrews [37] have demon-

28. Elman, R., and Graham, E.: The Pathogenesis of "Strawberry" Gallbladder (Cholesterosis of the Gallbladder), Arch. Surg. **24**:14 (Jan.) 1932.

29. Naunyn, B.: Klinik der Cholelithiasis, Leipzig, F. C. W. Vogel, 1892; A Treatise on Cholelithiasis, London, New Sydenham Society, 1896.

30. Ravdin, I. S., and Johnston, C. G.: Gallbladder: Recent Advances as Applied to Treatment, Pennsylvania M. J. **35**:357 (March) 1932. Ravdin, I. S.; Johnston, C. G.; Austin, J. H., and Riegel, C.: Studies of Gall-Bladder Function: Absorption of Chloride from Bile-Free Gall Bladder, Am. J. Physiol. **99**:638 (Feb.) 1932.

31. Andrews, E.; Schoenheimer, L. R., and Hrdina, L.: Etiology of Gall Stones: Clinical Factors and Role of Gall Bladder, Arch. Surg. **25**:796 (Oct.) 1932.

32. Lichtwitz, L.: Ueber die Bildung der Harn und Gallenstein, Ergebn. d. inn. Med. u. Kinderh. **13**:1, 1914; Zur Genese der Gallensteine, München. med. Wchnschr. **55**:629, 1908.

33. Gosset, A.; Bertrand, I., and Loewy, G.: La vésicule fraise, Progrès méd. **44**:1792 (Oct. 30) 1928.

34. Illingworth, C. F. W.: Cholesterosis of the Gall-Bladder: Clinical and Experimental Study, Brit. J. Surg. **17**:203 (Oct.) 1929.

35. Mackey, A.: Cholesterosis of the Gall Bladder, Brit. J. Surg **24**:570 (Jan.) 1937.

36. Dostal, L. E., and Andrews, E.: Etiology of Gall Stones: Effect of Diet on the Bile-Salt: Cholesterol Ratio, Arch. Surg. **26**:258 (Feb.) 1933.

37. Aronsohn, H. G., and Andrews, E.: Experimental Cholecystitis, Surg., Gynec. & Obst. **66**:748 (April) 1938.

strated that chemical cholecystitis may be set up by a high concentration of bile salts in the gallbladder and possibly in the blood stream. How, then, may one account for the concentration of cholesterol which may be found in gallbladder bile—100 to 2,000 mg. per hundred cubic centimeters? The hepatic bile contains little cholesterol, yet from ten to one hundred times its concentration is often seen in the gallbladder at operation, whereas the concentration of bile salts is seldom above ten times the concentration in the hepatic bile. While this finding may be cited as evidence that the cholesterol is secreted by the mucosa of the gallbladder, the work of Boyd,[25] Whitaker,[23] Sweet [38] and Wilkie and Doubilet [39] opposes such an assumption.

It is agreed that some, if not all, of the cholesterol in the bile is in a state of colloidal solution. The studies of Wieland and Sorg [40] showed that the bile salts, particularly the salts of desoxycholic acid, form addition compounds with fatty acids or cholestrol which increase the solubility of the latter. Verzár and Kúthy,[41] in particular, have stressed the importance of such compounds in favoring the intestinal absorption of lipoids and cholesterol. Other investigators, following Newman,[42] have stressed the importance of these compounds in keeping the cholesterol in the bile solution and have insisted that when the bile salt–cholesterol ratio falls below a critical level cholesterol is precipitated out of solution. It is further assumed that such precipitation leads to the formation of cholesterol calculi.

The bile salt-cholesterol ratio may be disturbed either by hepatic damage with a changed hepatic bile or by a differential absorption of cholesterol and bile salts in the gallbladder or bile ducts. Hammarsten [43] reported the bile salt–cholesterol ratio in the normal gallbladder to be 25:1. Newman,[42] who first emphasized the importance of this ratio in the pathogenesis of gallstones, stated that the critical ratio for

38. Sweet, J. E.: The Liesegang Phenomenon in Gall Stones, in Weiser, H. B.: Colloid Symposium Annual, New York, John Wiley & Sons, Inc., 1930, p. 249; Formation of Calculi, Ann. Surg. **101**:624 (Jan.) 1935.

39. Wilkie, A. L., and Doubilet, H.: Passage of Cholesterol Through the Mucosa of the Gallbladder, Arch. Surg. **26**:110 (Jan.) 1933.

40. Wieland, H., and Sorg, H.: Untersuchungen über die Gallensäuren, Ztschr. f. physiol. Chem. **97**:1, 1916.

41. Verzár, F., and von Kúthy, A.: Die Bedeutung der Gallensäuren für die Fettresorption, Biochem. Ztschr. **205**:369, 1929; Die Bedeutung der gepaarten Gallensäuren für die Fettresorption, ibid. **230**:451, 1931. Verzár, F.: Absorption of Fats, Nutrition Abstr. & Rev. **2**:441 (Jan.) 1933.

42. Newman, C.: Physiology of the Gall Bladder and Its Functional Abnormalities (Goulstonian Lecture), Lancet **1**:785 (April 15); 896 (April 29) 1933.

43. Hammarsten, O.: Darstellung der Gallensäuren und ihrer wichtigsten Abbauproduckte und ihr Nachweis, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1925, pt. 6.

the precipitation of cholesterol is 18:1. Andrews, Schoenheimer and Hrdina [31] placed the critical ratio at 13:1. Walsh and Ivy,[10] Walsh [9] and Dolkart, Jones and Brown,[44] in exhaustive experimental studies, have shown that fatty acids have a solvent action on cholesterol masses and on "mixed" gallstones. They concluded, therefore, that it is the concentration of fatty acids in the bile rather than that of bile salts that keeps the cholesterol in solution. Illingworth [34] Reinhold, Ferguson and Hunsberger [45] and Weiser and Gray,[46] on the other hand, did not attach significance to the presence of fatty acids, for they were unable to demonstrate fatty acids in bile from normal gallbladders in sufficient concentration to prevent the precipitation of cholesterol.

Phemister and his associates [47] reported that precipitates of calcium salts are formed in gallbladders only when a complete obstruction and a low grade chronic inflammation are present. They argued that since cholesterol is not found in such gallbladders the gallbladder cannot be the source of the cholesterol found in gallstones. Calcium salts, they concluded, represent a specific response on the part of the wall of an inflamed gallbladder.

Reported changes in the reaction of bile have not been consistently demonstrated in calculous gallbladders. Feldman, Morrison and Krantz,[48] reasoning from the observation that human cholesterol and "mixed" gallstones will dissolve when placed in the more acid gallbladder bile of the dog, concluded that the alkaline p_H of human hepatic bile, unchanged by the gallbladder, may be an important etiologic factor in the formation of gallstones. Reinhold, Ferguson and Hunsberger,[45]

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44. Dolkart, R. E.; Jones, K. K., and Brown, C. F. G.: Chemical Factors Concerned in the Formation of Gallstones, Arch. Int. Med. **62**:618 (Oct.) 1938; The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gall Stones, Am. J. Digest. Dis. & Nutrition **4**:587 (Nov.) 1937.

45. Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A.: Composition of Human Gall Bladder Bile and Its Relationship to Cholelithiasis, J. Clin. Investigation **16**:367 (May) 1937.

46. Weiser, H. B., and Gray, G. R.: Mechanism of Formation of Pure Cholesterol Gall Stones, Arch. Path. **17**:1 (Jan.) 1934.

47. Phemister, D. B.; Aronsohn, H. G., and Pepinsky, R.: Variation in Cholesterol, Bile Pigment and Calcium Salts Contents of Gallstones Formed in Gallbladder and in Bile Ducts with the Degree of Associated Obstruction, Ann. Surg. **109**:161 (Feb.) 1939. Phemister, D. B.; Day, L., and Hastings, A. B.: Calcium Carbonate Gallstones and Their Experimental Production, Ann. Surg. **96**:595 (Oct.) 1932.

48. Feldman, M.; Morrison, S., and Krantz, J. C., Jr.: Etiology of Gall Stones: Relationship of p_H of Bile to the Formation and Dissolution of Gall Stones, Am. J. Digest. Dis. & Nutrition **4**:13 (March) 1937. Feldman, M.; Morrison, S.; Carr, C. J., and Krantz, J. C., Jr.: Contribution to the Etiology of Gall Stones: A Study of the Hydrogen-Ion Concentration of Gall Bladder Bile and Its Effect upon Gall Stones, ibid. **4**:223 (June) 1937.

Reinhold and Ferguson,[49] Rous [50] and Weiser and Gray,[46] on the other hand, did not find that normal gallbladder bile has a higher hydrogen ion concentration than hepatic bile. They stated the belief that there is no marked change in the presence of an inflammation. Walsh [9] reported that an acid p_H allows cholesterol to stay in solution more readily but ascribed this to the presence of bile acids and to fatty acids which are known solvents of cholesterol. Dolkart, Jones and Brown [44] found no statistically significant difference in the relative solvent action on mixed stones of acid and alkaline bile secured from the ox, the dog or man.

The original hypothesis of Naunyn,[29] propounded in 1892, held that gallstones are the result of an infection in the gallbladder or bile ducts. Nearly all subsequent theories have presupposed that some injury, inflammation or chemical change of the bile in the gallbladder is the initiating cause for the formation of stones. Moynihan [4] has stated, "the gall stone is a tombstone erected to the memory of the organism within it." The early clinical researches indicated that most gallbladders with stones are infected. Gordon-Taylor and Whitby [51] found 70 per cent infected; Moynihan found 95 per cent infected, and Walton [52] found 70 per cent infected. Recent clinical studies by various investigators have shown wide variation in the incidence of bacteria-yielding cultures of material from calculous gallbladders. Moynihan,[4] Griffith and Kipp,[53] Patey,[13] Walton,[52] Albeaux-Fernet [54] and Walters,[55] as well as many others, have concluded from a clinical standpoint that infection of the gallbladder is a basic cause for stone formation, since it causes changes in the mucosa with resulting functional disturbances, stasis and colloidal changes favoring precipitation. All have agreed that pure cholesterol stones are metabolic in origin, thus differing from the mixed, or common, gallstones. Potter and Mann,[56] Illing-

49. Reinhold, J. G., and Ferguson, L. K.: Reaction of Human Bile and Its Relationship to Gall Stone Formation, J. Exper. Med. **49**:681 (April) 1929.

50. Rous, P.: Physiological Factors in the Genesis of Gall Stones, Proc. Inst. Med. Chicago **7**:33 (April 15) 1928.

51. Gordon-Taylor, G., and Whitby, L. E. H.: A Bacteriological Study of Fifty Cases of Cholecystectomy with Special Reference to Anaerobic Infections, Brit. J. Surg. **18**:78 (July) 1930.

52. Walton, J.: The Formation and Treatment of Calculi in the Biliary Ducts and Gall Bladder, Surg., Gynec. & Obst. **64**:257 (Feb.) 1937.

53. Griffith, J. P., and Kipp, H. A.: Remarks on the Etiology and Treatment of Cholecystitis, Pennsylvania M. J. **35**:362 (March) 1932.

54. Albeaux-Fernet, M.: Les hypothèses pathogéniques de la lithiase biliaire, Gaz. méd. de France (supp. Gastro-enterol.) [**43**]:3 (Nov. 15) 1936.

55. Walters, W.: Pathological Physiology of Stone in the Common Duct: Clinical and Surgical Significance, Surg., Gynec. & Obst. **63**:417 (Oct.) 1936.

56. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, Am. J. M. Sc. **171**:202 (Feb.) 1926.

worth,[57] Ravdin and Johnston [30] and Furth [58] have reached the same general conclusion after animal experimentation and clinical studies. Illingworth stated the belief that the Lichtwitz [32] theory of electropositive and electronegative charges, with the inflammatory exudate acting as an electronegative substance, may explain the "trigger mechanism" which causes the cholesterol to precipitate.

On the other hand, Aschoff and Bacmeister,[59] Rovsing [21] and Crile,[19] after both clinical and experimental studies, concluded that the infection is the consequence and not the cause of gallstones. MacCarty [60] made a statistical study of 21,523 gallbladders but was unable to determine which is the primary factor, whereas Walters [55] and Ravdin and Johnston [30] stated the belief that either may be the initial condition. It is debatable, therefore, whether this question can be answered by clinical research alone.

Aschoff and Bacmeister's assumption that neither infection nor a product of infection is the cause of stones arose from their experimental and clinical studies on the precipitation of cholesterol in the presence of stasis within the gallbladder. They maintained that this stasis, regardless of the cause, favors changes in solubility due to overconcentration of the cholesterol with resultant precipitation, the precipitated cholesterol being the nucleus of the stone. The fact that many pathologic conditions, some of them neurogenic, result in biliary stasis and an increased concentration of the bile within the gallbladder has been established by Westphal,[61] Ivy,[16] Whitaker [23] and Greene, Twiss and Carter.[62] Though McMaster and Elman,[63] Boyden,[64] Whitaker [65]

57. Illingworth, C. F. W.: The Formation of Calculi, Edinburgh M. J. **43**: 481 (Aug.) 1936.

58. Furth, O.: Pathologische Physiologie der Aufbau der Gallensteinen, Wien. klin. Wchnschr. **50**:629, 1937.

59. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909; Lectures on Pathology, New York, Paul B. Hoeber, 1924.

60. MacCarty, W. C.: The Gallbladder and Its Diseases, Proc. Staff Meet., Mayo Clin. **11**:805 (Dec. 16) 1936.

61. Westphal, K.: Muskelfunktion, Nervensystem und Pathologie der Gallenwege, Ztschr. f. klin. Med. **96**:22, 1923; Die Bewegungs- und Resorptionsstörungen an den Gallenwegen und ihre Gefahren, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1932, Knog. 44, p. 354.

62. Greene, C. H.; Twiss, J. R., and Carter, R. F.: Biliary Stasis, Am. J. Digest. Dis. & Nutrition **3**:622 (Nov.) 1936.

63. McMaster, P. D., and Elman, R.: On the Expulsion of Bile by the Gall Bladder and a Reciprocal Relationship with the Sphincter Activity, J. Exper. Med. **44**:173, 1926.

64. Boyden, E. A.: Sphincter of Oddi in Man and Certain Representative Mammals, Surgery **1**:25 (Jan.) 1937.

65. Whitaker, L. R.: The Mechanism of the Gallbladder and Its Relation to Cholelithiasis, J. A. M. A. **88**:1542 (May 14) 1927.

and Ravdin and Johnston [30] could demonstrate no definite reciprocal relation between the sphincter of Oddi and the gallbladder of the dog, according to Berg and Jobling,[66] Ivy [16] and Meltzer [67] there is much indirect evidence that such a relation does exist.

Whitaker [65] has demonstrated the formation of pseudostones in the gallbladder of the dog by inducing stasis in the absence of infection or damage to the liver. Meltzer,[67] von Babarczy [68] and Halpert [69] have also made a strong case for stasis. Ravdin and Johnston,[30] Walters,[55] Walsh,[9] Moore [70] and also Rous [50] have shown that stasis is at least an accessory factor in the formation of stones. Cooper and Illingworth [71] were unable to reproduce Whitaker's experimental results and so agreed with Pavel,[72] Furth [58] and many others that stasis is not a probable cause for the formation of gallstones.

The observation that pure cholesterol stones crystallize according to the laws of colloids has led to the "colloidal theory" of stone formation, supported extensively by Sweet,[38] Weiser and Gray [46] and Shade.[73] Sweet maintained that "under normal conditions, whatever passes into the gallbladder through the cystic duct, never passes out again through the cystic duct." He made synthetic stones from gelatin, chromates and silver nitrate and found them to be structurally similar to the cholesterol stones in the human gallbladder. The Liesegang phenomenon, with rhythmic precipitation of calcium and pigment, he concluded, explains the laminated appearance on section of cholesterol and mixed gallstones. Phemister and his associates,[47] on the other hand, insisted that the deposition of calcium is evidence of inflammatory changes in the wall of the gallbladder. They stated that when a gallstone consists of a

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66. Berg, B. N., and Jobling, J. W.: The Effect of Division and Transplantation of the Common Duct upon the Gall Bladder Function, Proc. Soc. Exper. Biol. & Med. **24**:434 (Feb.) 1927. Berg, B. N.: Gall Bladder Function After Division of the Common Duct, Surg., Gynec. & Obst. **46**:464 (April) 1927.

67. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathologic Factor in Diseases of the Bile Ducts and the Gall Bladder, Am. J. M. Sc. **153**:469 (April) 1917.

68. von Babarczy, M.: Die Bedeutung der Cholesterins in der Diätetik der Cholecystopathien, Ztschr. f. klin. Med. **133**:656, 1938.

69. Halpert, B.: New Aspects of Formation and Classification of Gall Stones, Arch. Path. **6**:623 (Oct.) 1928.

70. Moore, S. W.: Intramural Formation of Calculi, Arch. Surg. **34**:410 (March) 1937.

71. Cooper, G. H., and Illingworth, C. F. W.: Experimental Study of the Factor of Biliary Stasis in the Production of Gall Stones, Surg., Gynec. & Obst. **46**:658 (May) 1928.

72. Pavel, I.: Du rôle peu important de la stase dans la pathogénie de la lithiase biliaire (avec une critique de la dyskinésie et quelques considérations thérapeutiques), Presse méd. **43**:1565 (Oct. 9) 1935.

73. Shade, H., cited by Sweet.[38]

central nucleus of cholesterol with several rings of calcium and pigment around the periphery, this structure is evidence for the occurrence of successive attacks of obstruction and active cholecystitis in a gallbladder which initially contained a pure cholesterol stone of metabolic origin. At present these opposing views of Phemister and Sweet are irreconcilable.

Pancreatic ferments have been found in many calculous gallbladders removed at operation, and it has been assumed that the ferments were regurgitated through the common and cystic ducts into the gallbladder. Sweet,[27] Crile [19] and Wolfer [74] have concluded that this may be a factor leading to the precipitation of cholesterol. Colp, Gerber and Doubilet [75] stated the belief that such a reflux was the cause of severe acute cholecystitis in 3 cases which they reported. Andrews and his co-workers were able to change the bile salt–cholesterol ratio in the gallbladders of dogs by injecting pancreatic fluid into them. The common finding of pancreatic ferments in gallbladders removed at operation warrants further investigation.

PURPOSE OF THIS STUDY

The present survey was made to see whether in a series of patients with and without gallstones and with either disease or dysfunction of the gallbladder the operative findings could be correlated with the results of a detailed chemical and bacteriologic study in such a way as to throw additional light on the applicability of the different theories of origin of the gallstone. All patients were studied in the clinic for patients with disease of the gallbladder. In the case of each there was a preoperative period of study; pathologic, bacteriologic and chemical examinations were made of the operative specimens, and there was careful clinical and laboratory observation during the postoperative period of follow-up.

We recognize that this analysis was made on patients long after the stones had been formed, in some instances probably twenty-five years later. It is probable, therefore, that the factors present at the time the stones were formed were no longer present or active at the time of the study. We can only point out the difficulties of determining the exact pathogenesis of the stones in this or in any similar series of cases and the inapplicability of most of the aforementioned theoretic causes. If it were possible experimentally to produce all types of stones under conditions comparable to those in the human organism or to follow patients before and after the formation of the stones, one could more readily solve the problems of their formation.

74. Wolfer, J. A.: Further Evidence That Pancreatic Juice Reflux May Be the Etiologic Factor in Gallbladder Disease, Ann. Surg. **109**:187 (Feb.) 1939.

75. Colp, R.; Gerber, I. E., and Doubilet, H.: Acute Cholecystitis Associated with Pancreatic Reflux, Ann. Surg. **103**:67, 1936.

METHOD AND RESULTS

Duodenal Drainage.—During the past nine years, 239 operative cases from the clinic for patients with disease of the gallbladder have been studied in this fashion. In the majority of cases the preoperative period of observation was from one to thirty-six months. In all cases duodenal drainage was done and a chemical examination of the blood was made before operation. Drainage was done according to the method described by Twiss and Phillips.[76] The duodenal contents were examined for concentration of bile salts, cholesterol content, activity of pancreatic ferment and microscopic evidence of crystals, pus cells and epithelial debris. A bacteriologic examination of the duodenal contents was made. A "fasting gastric specimen" was usually examined for hydrochloric acid content at the beginning or at the completion of the duodenal drainages. Specifically, this study on duodenal drainage was done to correlate the preoperative with the operative findings and to establish any relation which might exist between the material obtained by duodenal drainage and the presence of cholelithiasis.

When the average results found in this series of preoperative duodenal drainages were correlated with the presence or absence of stones (table 1), there was no difference in the bile salt concentration, the cholesterol content and the presence

TABLE 1.—*Average Results in Specimens Obtained by Duodenal Drainage*

	Bile Salts, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Percentage with Crystals	Percentage with Organisms
Patients with noncalculous gallbladders.....	2,000	42	86.2	14
Patients with calculous gallbladders.....	2,080	89	75.6	54

or absence of crystalline sediment. Evidence of infection in the biliary tract as revealed by culture of the duodenal contents (contaminated specimens excluded) was, however, found in more than half the gallbladders with stones and in only 14 per cent of those without stones.

The presence of crystals has been described as indicative of the presence of stones. That this is a misleading conclusion is apparent when the operative findings in this series of cases are correlated with the results of duodenal drainage. In 24.4 per cent of the patients with stones, no crystals were found in the preoperative duodenal drainage, but crystals were present in 86.2 per cent of the patients without stones. While the presence or absence of crystals has no specific diagnostic import where stones are concerned, their presence is definitely indicative of stasis in the biliary tract. This is particularly evident in patients with dyskinesia of the gallbladder, who frequently show exacerbation of their symptoms at the same time that duodenal drainage shows the presence of crystals.

Blood Chemistry.—Preoperative studies of the blood chemistry were made in every case. Repeated studies were done in cases observed for more than one month. This included the determination of the total cholesterol, the cholesterol esters, the icteric index and the van den Bergh reaction. For a time other tests of liver

76. Twiss, J. R., and Phillips, C. H.: Bacteriological Findings in Disease of the Biliary Tract: Improved Method of Obtaining Cultures of Bile by Duodenal Drainage, Am. J. Digest. Dis. & Nutrition **2**:663 (Jan.) 1935.

function were performed, but these were abandoned in favor of determination of the cholesterol–cholesterol ester ratio, which was studied to estimate the hepatic reserve and to evaluate the role of hypercholesteremia in the formation of gallstones.

During the period of preoperative observation (table 2) the average cholesterol content of the blood was equal in patients with stones and in those without. There were wide variations, but when a further analysis was made of those with hypercholesteremia (220 mg. per hundred cubic centimeters or more) the same relation continued to exist. A comparable number in each group had the opposite condition, that is, hypocholesteremia (160 mg. per hundred cubic centimeters or less). Operation had little effect on the general level of blood cholesterol. Only 40 per cent of the patients with stones showed a change of more than 10 per cent in the values for blood cholesterol, as against a 43 per cent incidence of such change in the group without stones. The values for blood cholesterol in an individual case may vary widely, but when mean results are determined for a group of cases they remain remarkably constant.

TABLE 2.—*Blood Cholesterol of Patients Operated on for Disease of the Gallbladder (239 Patients)*

	Calculous	Noncalculous
Average value for blood cholesterol on admission to clinic....	207 mg./100 cc.	204 mg./100 cc.
Average value for blood cholesterol immediately before operation	204 mg./100 cc.	200 mg./100 cc.
Average value for blood cholesterol 1 to 6 months after operation	206 mg./100 cc.	206 mg./100 cc.
Percentage showing hypercholesteremia preoperatively (220 mg./100 cc. or more).....	29	29
Percentage showing hypercholesteremia postoperatively (200 mg./100 cc. or more).....	31	34
Percentage showing no change (less than 10 mg./100 cc.) in postoperative period	60	57

Roentgen Study.—A cholecystogram of each patient was made by the Graham-Cole technic. The diagnosis of stones was accurate in cases in which the gallbladder was visualized. Since the use of the double dye method of visualization an accurate roentgen diagnosis has been made in 95 per cent of cases of stone in which the gallbladder concentrates dye. Gallbladders that fail to visualize by the double dye method are gallbladders with obliterated lumens and containing stones or gallbladders with intermittent complete obstruction (hydrops) of the cystic duct.

During the past nine years, approximately 2,600 patients have been examined and followed in the clinic for patients with disease of the gallbladder without the known development of stones in any who did not have them on admission to the clinic. Twiss and Barnhard [77] concluded that this was due to the control of stasis by therapeutic means and to the dietary control of the cholesterol intake.

Operative Material.—At operation the gallbladder was removed and specimens of bile were obtained for chemical, microscopic and bacteriologic examination. (The incidence of the various pathologic types of bile is given in table 3.) Cultures were made of the remaining bile, of material from the wall of the gallbladder,

77. Twiss, J. R., and Barnard, J. H.: Disease of Biliary Tract Associated with Disturbances in Cholesterol Metabolism, J. A. M. A. **111**:990 (Sept. 10) 1938. Twiss, J. R., and Greene, C. H.: Dietary and Medical Management of Diseases of the Gall Bladder, ibid. **101**:1841 (Dec. 9) 1933.

of material from the cystic lymph node and of the common duct bile. A culture of any of these which yielded bacteria was considered evidence of viable organisms in the gallbladder. The results of the cultures for the various types of disease of the gallbladder encountered are given in table 4.

It is evident that gallbladders which showed a normal concentration of dye on preoperative roentgen examination rarely showed organisms either in their bile or in the wall. Furthermore, only 38 per cent of these gallbladders with stones showed evidence on microscopic examination of previous mucosal inflammation or infection.

The values for bile salts and bile acids in the gallbladders were determined by both the Reinhold-Wilson [78] and the Aldrich-Bledsoe [79] methods. These are both colorimetric methods, and their use has been challenged because of nonspecificity

TABLE 3.—*Pathologic Classification of Gallbladders Removed*

Specimens normal or showing evidence of dysfunction without stones	23
Specimens showing chronic cholecystitis without stones	17
Total noncalculous gallbladders	40
Specimens showing evidence of metabolic disturbance or dysfunction with stones	29
Specimens showing chronic cholecystitis with stones	159
Specimens showing acute cholecystitis	11
Total calculous gallbladders	199

TABLE 4.—*Incidence of Cultures Yielding Bacteria (Gallbladder Removed at Operation)*

	Calculous Gallbladders, Percentage	Noncalculous Gallbladders, Percentage
Dyskinesia*	16	13
Chronic cholecystitis	40	25
Acute cholecystitis	83	..

* "Dyskinesia" represents the condition of gallbladders with a relatively normal pathologic picture and a normal concentration of the dye in preoperative roentgen examination.

and the effect of possible interfering substances in the bile. They do not distinguish between conjugated and free bile acids and do not show the presence of desoxycholic or other bile acids or their derivatives which do not contain the cholic acid group. The results (table 5), however, are of interest from the comparative standpoint. The results show wide fluctuations but indicate that the functioning gallbladder in general produces a greater concentration of bile salts than does the nonfunctioning gallbladder. The greatest concentration was found in the presence of stasis. The inflamed, thickened, infected gallbladder either failed to concentrate bile salts or absorbed them.

The cholesterol content of gallbladder bile also varied to a great degree. Table 6 is a study on cholesterol content similar to the one on bile salts. Determinations

78. Reinhold, J. G., and Wilson, D. W.: The Determination of Cholic Acid in Bile, J. Biol. Chem. **96**:637 (June) 1932.

79. Aldrich, M., and Bledsoe, M. S.: Studies in the Metabolism of Bile: I. A Quantitative Pettenkofer Test Applicable to the Determination of Bile Acids in Blood, J. Biol. Chem. **77**:519 (May) 1928.

of the cholesterol content were performed according to the method of Lieboff.[80] It was noted that as the severity of the pathologic changes found at operation increased the cholesterol content of the gallbladders decreased. In calculous gallbladders that were functioning, i. e., that concentrated and emptied the dye on roentgen examination, the cholesterol content was much higher than in those shown by the roentgen rays to be nonfunctioning. This is interpreted as indirect evidence

TABLE 5.—*Bile Salt Content of Calculous and Noncalculous Gallbladders*

	Average Bile Salt Concentration, Mg./100 Cc.	Percentage 25% Below Mean Average	Percentage 25% Above Mean Average
Noncalculous gallbladders			
Dyskinesia and chronic cholecystitis.....	3,154 ± 300	40	21
Calculous gallbladders	3,910 ± 300	35	16
(*a*) Dyskinesia	4,780 ± 150	14	7.6
(*b*) Chronic cholecystitis	3,745 ± 400	44	20
(*c*) Obliterative cholecystitis	1,785 ± 360	62	12

TABLE 6.—*Cholesterol Content of Calculous and Noncalculous Gallbladders*

	Average Concentration, Mg./100 Cc.	Percentage with Concentration 25% Below Mean Average	Percentage with Concentration 25% Above Mean Average
Noncalculous gallbladders			
Dyskinesia and chronic cholecystitis.....	475 ± 60	22	33
Calculous gallbladders	573 ± 125	22	32
(*a*) Dyskinesia	720 ± 130	15	28
(*b*) Chronic cholecystitis	540 ± 140	25	32
(*c*) Obliterative cholecystitis	253 ± 30	12	50

TABLE 7.—*Bile Salt–Cholesterol Ratio in Calculous and Noncalculous Gallbladders*

	Percentage wtih Ratio Less than 18:1	Percentage with Ratio More than 18:1	Average Ratio
Noncalculous gallbladders			
Dyskinesia and chronic cholecystitis.....	80	20	7.7:1
Calculous gallbladders	86	14	7.5:1
(*a*) Dyskinesia	92	8	6.5:1
(*b*) Chronic cholecystitis	80	20	9.7:1
(*c*) Obliterative cholecystitis	88	12	8.7:1

of the concentrating power of the normal gallbladder for cholesterol. Another interpretation is that advanced by Elman and Graham,[28] who stated the belief that the normal gallbladder secretes cholesterol and that this function is impaired when the gallbladder is damaged.

The bile salt–cholesterol ratios in the different types of cases are given in table 7. In the majority of cases, whether or not stones were present, the ratio was below the level at which precipitation usually is assumed to occur. The analytic method

80. Lieboff, S. L.: A Simplified Method for Cholesterol Determination in Blood, J. Biol. Chem. **61**:177, 1924.

used for determining the value for bile salts affects the absolute values obtained, so that these ratios are not strictly comparable with many others reported in the literature. It is significant that the ratio was low for as many patients without stones as with stones.

The significance of pancreatic ferments in the gallbladder bile has been variously interpreted. In this series of noncalculous gallbladders the pancreatic ferments were found in 53 per cent of all gallbladders and in 59 per cent of calculous gallbladders. The Myers and Fine[81] methods of determination of the presence of ferment were used, and in each instance two or three ferments were considered necessary to indicate "positive" results. This stand was taken to obviate the misinterpretation of the finding of amylase in the gallbladder, as this ferment may be found in tissues totally dissociated from the pancreas.

Microscopic examination of the gallbladder bile revealed no significant variation between the calculous and the noncalculous gallbladders. In gallbladders with

TABLE 8.—*Summary of a Study of 100 Consecutive Gallbladders Removed at Operation with Complete Preoperative Work-Up and Minute Postoperative Examination*

	Average Age of Patients, Yr.	Average Duration of Symptoms, Yr.	Average Bile Salt Concentration, Mg./100 Cc.	Average Cholesterol Content, Mg./100 Cc.	Bile Salt-Cholesterol Ratio			Percentage of Cultures Yielding Bacteria	Percentage with Microscopic Evidence of Previous Infection	Percentage with Hypercholesteremia	Percentage with Evidence of Damage to Liver	Percentage with Pancreatic Ferments
					Percentage Less than 18:1	Percentage More than 18:1	Average Ratio					
Noncalculous gallbladders	39	6	3,154	475	80	20	7.7:1	13	26	20	40	53
Calculous gallbladders (total)	40.6	7	3,910	573	86	14	7.5:1	34	78	29	16	60
(*a*) Dyskinesia	37	5	4,780	720	92	8	6.5:1	11	38	33	15	48
(*b*) Chronic cholecystitis	41	5.5	3,745	540	80	20	9.7:1	33	100	30	23	67
(*c*) Obliterative cholecystitis as shown by roentgen examination	51	12	1,785	253	88	12	8.7:1	100	100	12	0	50

acute inflammation (generally those with stones), pus, epithelial debris and mucus were found. Crystals in the gallbladder bile were present in 94 per cent of calculous gallbladders and in 73 per cent of noncalculous gallbladders. Microscopic examination of the stones gave no noteworthy information except that the gallbladders with a single cholesterol stone usually showed no evidence of previous inflammation and that material from them was sterile on culture in nearly every instance.

A summary of the possible causes for the gallstones found in our series is given in table 8. The incidence of these factors in calculous cholecystitis is in contrast to their incidence in noncalculous gallbladders. The factors summarized are (1) the age of the patients, (2) the duration of the active symptoms, (3) the bile salt concentration, (4) the cholesterol content, (5) the bile salt-cholesterol ratio, (6) the organisms on culture, (7) the evidence of a previous inflammation,

81. Myers, V. C., and Fine, M. S.: A Consideration of the Chemical Methods Employed in Medical Diagnosis, Post-Grad. M. J. **28**:384, 1913. Myers, V. C.: Animal Diastases, J. Biol. Chem. **29**:179 (March) 1917.

(8) the presence of hypercholesteremia during the preoperative period of study, (9) evidence of hepatic damage and (10) the presence in the gallbladder of pancreatic ferments.

COMMENT

Before discussing the application of specific theories to the cause of the stones found in our series, it is well to call attention to the patients' ages and the duration of active symptoms. These factors were nearly equal in the calculous and the noncalculous groups and therefore seem to have no bearing on the problem. The variation in action of such factors as were found to be equally prevalent in both groups cannot be attributed to a short interval during which they had been acting. The factors of age and duration of symptoms were significant only in gallbladders whose lumens were obliterated. This is what may be anticipated in cases of severe long-standing disease.

In this series of cases the level of blood cholesterol apparently did not play a role in the causation of stones. There is no way of determining what this factor may have been at the time the stones were first formed, but it was evident that an appreciable variation from normal did not persist; furthermore, the preoperative and postoperative levels of blood cholesterol were remarkably equal in the series as a whole. We found the same wide variations in the values for blood cholesterol that have always been an unexplained factor in such studies (Riegel, Ravdin and Rose [12]). During the period of study, there was nearly as high an incidence of hypercholesteremia in patients without as in those with stones (20 per cent and 29 per cent respectively). Moreover, the general level of blood cholesterol as seen in our operative patients was that seen generally in our clinic on routine examination of the blood of patients without stones or organic disease of the gallbladder. It was slightly higher than that given in similar reports in the literature. Von Babarczy [68] Twiss and Barnard,[77] Moynihan,[4] Whitaker,[23] Dewey [6] and McMaster [82] have stated the belief that the level of blood cholesterol can be controlled by diet and that dietary control may reduce the incidence of stones. It was noted that patients with hypercholesteremia who were observed for a time on a low cholesterol diet showed an appreciable reduction in the level of blood cholesterol. Because of the wide fluctuation of values for blood cholesterol in the same patient (Walsh;[9] Dostal and Andrews;[36] Fox [83]) and the general results in this series of cases, we do not believe that the general level of blood cholesterol is materially influenced by the diet except over long periods. The fact, furthermore, that the average value for blood cholestrol was

82. McMaster, P. D.: Studies on Total Bile: Influence of Diet upon the Output of Cholesterol in Bile, J. Exper. Med. **40**:25 (July) 1924.

83. Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolism, Quart. J. Med. **21**:107 (Oct.) 1927.

the same for the noncalculous patients as for those with stones confirms this belief and also the observations of Campbell.[84] It was particularly evident in this investigation that a study of the blood at the time of operation is futile in arriving at a solution of the possible cause of the stones found in the gallbladder.

It has been mentioned that hepatic damage causes a change in the character of the bile which possibly may favor the formation of gallstones. A careful study of hepatic function preoperatively and a study of the liver by observation and biopsy at the time of operation have shown that nearly 40 per cent of noncalculous patients had some evidence of damage to the liver, as against only 16 per cent of calculous patients. No conclusion may be drawn from this finding except that the value of such functional studies in determining the cause of the gallstones is minimal. It must not be assumed from these findings that hepatic disease generally is more frequent in noncalculous than in calculous disease of the gallbladder, for in many instances a cholecystectomy was performed because of evidence of hepatic disease which was thought to be associated with chronic cholecystitis. This practice has been discontinued in the clinic during recent years.

A comparison of the chemical composition of bile from noncalculous with that of bile from calculous gallbladders does not justify the belief that a decrease in the bile salt–cholesterol ratio favors the formation of gallstones. In only 20 per cent of the noncalculous gallbladders did the ratios exceed 18:1, and in only 26 per cent did it exceed 13:1. In nearly 80 per cent of all noncalculous gallbladders the concentration of bile salts in the bile was below that ordinarily considered necessary to keep cholesterol in solution, and yet stones were not formed. Among the cases of calculus the ratios in 14 per cent were sufficient to keep cholesterol in solution, i. e. more than 18:1, and in 22 per cent the ratios were above 13:1. On this theory we found the average ratio in cases in which no stones were present to be 7.7:1, and that of cases in which stones were present, 7.5:1. It is evident that while bile salts may help to keep cholestrol in solution, changes in this purely chemical factor cannot be held accountable for the stones seen in this series of cases.

In this series there was a very low incidence of infection in noncalculous functioning gallbladders. In addition, only 1 in 4 gallbladders showed any pathologic evidence of a previous inflammation. The same low incidence of both findings was seen in the calculous gallbladders with normal function as shown by the roentgen rays. This contradicts the theory of Albeaux-Fernet [54] that transient infections, causing changes in the wall of the gallbladder but completely subsiding, are the cause of gallstones found in functioning gallbladders. The stones found in

84. Campbell, J. M. H.: Cholesterol in Blood in Cases of Gall-Stones, Quart. J. Med. **18**:123 (Oct.) 1924.

functioning gallbladders in this series frequently were cholesterol stones, but 60 per cent of all the stones in such gallbladders were "mixed" stones of the type usually ascribed to inflammation. The incidence of cultures yielding bacteria and of inflammatory evidence increased with the severity of the general process. Cultures of material from gallbladders with obliterated lumens yielded bacteria in nearly every instance. Differences in the proportionate number of such cases in the series perhaps accounts for the low incidence of infection in this series of cases as compared with the results reported by earlier investigators. From these findings it appears reasonable to assume that in many instances the stones preceded the infection, their presence acting as an irritant and so providing a means for the entry of bacteria into the wall of the gallbladder. Only 33 per cent of patients with "early cholecystitis" with or without stones showed either bacteriologic or pathologic evidence of previous or present inflammation or infection.

Stasis was a finding common to almost all the gallbladders in this series. Stasis was diagnosed preoperatively by the finding of a dense concentration of the dye in the cholecystogram by a delay in evacuation after a fatty meal and by the obtaining of concentrated bile with crystalline sediment on duodenal drainage. At operation this was generally confirmed by finding crystals in the gallbladder bile. This would seem a strong argument for stasis as a cause of gallstones were it not that the incidence of stasis as here defined was as great in the noncalculous gallbladders as in those with stones. As nearly as could be determined from the symptoms, stasis had been present for as long a period in the one type as in the other. Bile stasis was the one factor present in cases with stones that did not show evidence of past or continuing infection. In gallbladders with impaired visualization on roentgen examination and with evidence of a past or continuing infection, crystals and other evidence of stasis were invariably present. It could not of course be determined which was the primary condition.

The results of our study on pancreatic ferments in operative gallbladders were interesting but inconclusive. This possible factor in the formation of gallstones has received little attention in the literature. It merits a further study, for the anatomic relation existing between Wirsung's duct, the common duct and the ampulla of Vater allows pancreatic reflux into the gallbladder to take place in many patients. It is here that spasm of the sphincter may play a role in producing not only stasis in the biliary tract but pancreatic reflux. In this series, such a reflux was suggested by the finding of pancreatic ferments in the bile at operation in 53 per cent of the noncalculous gallbladders and in 59 per cent of those with calculi. A further study on pancreatic reflux, especially when correlated with a deficiency of fatty acids and saponifiable substances, is desirable.

SUMMARY

The study of this series of cases has served to emphasize the difficulty of determining the cause and pathogenesis of gallstones solely by a study of the patient at the time of operation. If the deposition of a calculus depends on the concomitant action of several different factors, the period of calculus formation may be limited, and a study of the patient one to twenty-five years later will fail to present the true picture of the conditions determining the deposition of the stone. It must also be recognized that the different types of gallstones may have different causes. When the various factors theoretically advanced as causes of gallstones are studied and correlated, no single factor or combination of factors satisfactorily explains the stones found in this series of cases.

The findings in this study furnish presumptive evidence that the composition of either the hepatic bile or of that obtained by duodenal drainage is not related to the changes in the chemical composition of the blood and that the cholesterol content of the gallbladder as determined at operation is not related to cholesterol content of the blood. Furthermore, this study has shown that the bile salt–cholesterol ratio is widely variable in all types of pathologic changes of the gallbladder and is often very low even in noncalculous gallbladders; that hypercholesteremia as determined by preoperative studies of the blood is not related to the presence of stones, and that pancreatic ferments are as common in noncalculous gallbladders as in those with calculi.

We were unable to show that there was any difference in the incidence of stasis in the cases in which gallstones were present and its incidence in the cases in which there were no stones. In 25 per cent of cases in which gallstones were present, stasis was the only one of the factors considered in the pathogenesis of stones which could be demonstrated. There is a strong presumption, therefore, that stasis was of importance in the formation of gallstones, but other, unknown factors must also have been in operation, for 86 per cent of the noncalculous gallbladders also showed evidence of stasis.

In 24 cases there were gallstones unassociated with any bacteriologic or pathologic evidence of infection or inflammation. This group of cases is evidence that infection is not necessary to the formation of stones and presumptive evidence that in many cases stones precede infection of the gallbladder.

TREATMENT OF VARICOSE VEINS

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Recent advances in the knowledge of varicose veins have emphasized the importance of three factors, namely, careful diagnosis, proper selection of cases and adequate therapeutic procedures. A systematized method of evaluating, selecting and treating the patients is therefore essential. At the University Hospitals the following concepts have proved valuable in relieving the greatest number of patients with varicose veins.

ANATOMIC CONSIDERATIONS

The usual anatomic positions of the venous components in the lower extremity are illustrated in the accompanying diagram.[1] The deep veins are the anterior tibial, posterior tibial, peroneal, popliteal and femoral. The superficial veins are the long saphenous and the short saphenous with their many tributaries, including the accessory branches entering the saphenous fossa. The communicating veins connect the superficial and the deep veins. There are usually one to three communicating veins in the thigh and as many as fifteen to thirty in the leg.[2] Blood normally flows upward through the superficial and deep veins. The superficial veins empty their blood into the deep veins at the junction of the long saphenous vein with the femoral vein, at the junction of the short saphenous vein with the popliteal vein and through the various communicating veins. Under normal conditions venous valves prevent a reflux of blood when the patient is in the upright position.

PATHOLOGIC PICTURE

Dilatation of superficial veins may be due to one or more of the following factors: congenital weakness of the venous walls or valves, obstruction of the deep veins, thrombophlebitis, pregnancy, trauma, tight clothing and prolonged standing. Whenever the varicose state develops, the venous valves become incompetent and a reflux of blood occurs.

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1. Edwards, E. A.: The Treatment of Varicose Veins: Anatomical Factors of Ligation of the Great Saphenous Vein, Surg., Gynec. & Obst. **59**:916-928 (Dec.) 1934.

2. Linton, R. R.: The Communicating Veins of the Lower Leg and the Operative Technic for Their Ligation, Ann. Surg. **107**:583-593 (April) 1938.

Patients with varicose veins have been classified for diagnostic and therapeutic purposes according to the location of the venous insufficiency, as follows:

Group I. Patients with deep venous obstruction with compensatory dilatation of any or all of the superficial veins.

Group II. Patients with incompetence of the valves in a dilated long saphenous vein.

Group III. Patients with incompetence of the valves in the dilated long saphenous vein and in the communicating veins of the thigh.

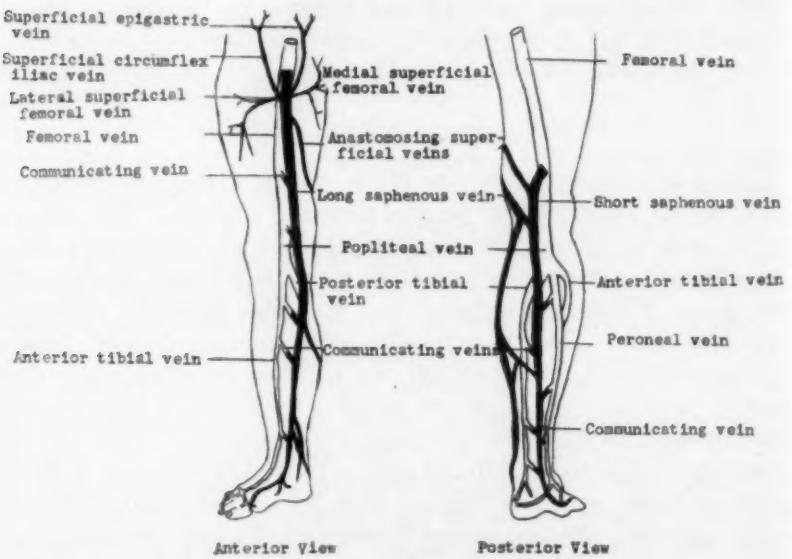

Diagram of the venous components in the lower extremity.

Group IV. Patients with incompetence of the valves in the dilated long saphenous vein and in the communicating veins of the leg.

Group V. Patients with incompetence of the valves in the dilated communicating veins of the thigh with involvement of the long saphenous vein below the femorosaphenous junction but with no influx of blood through the femorosaphenous junction.

Group VI. Patients with incompetence of the valves in the dilated communicating veins of the thigh without involvement of the long saphenous vein.

Group VII. Patients with incompetence of the valves of the dilated long saphenous vein with secondary dilatation of the short saphenous vein below the popliteosaphenous junction but with no reflux of blood from the popliteal to the short saphenous vein.

Group VIII. Patients with incompetence of the valves in only the dilated short saphenous vein.

Group IX. Patients with incompetence of the valves in both the long and the short saphenous veins with a reflux of blood through the femorosaphenous and the popliteosaphenous junction respectively.

Group X. Patients with incompetence of the valves in the dilated communicating veins of the leg.

Group XI. Patients with incompetence of the superficial venous walls with simple dilatation but no incompetence of the valves in any of the veins.

EXAMINATION AND DIAGNOSTIC TESTS

The examination of the patient must reveal in which of the aforementioned groups he can be placed. Various diagnostic procedures are used for identifying the dilated veins, for evaluating the patency of the deep veins and for locating the incompetent valves or "blow-out" points.

Inspection of the extremities with the patient standing in a good light will usually reveal the size and distribution of the varices. Dilatations directly related to the long saphenous vein are located on the medial aspect of the thigh and leg; however, much anatomic variation is noted with different patients. Varices related to an incompetent short saphenous vein are found on the posterolateral surface of the leg. Varices which appear to originate on the lateral aspect of the thigh and leg are often associated with obstruction of the deep veins.

The Schwartz test, which is performed by palpating the long or the short saphenous vein with one hand while percussing the varicosed veins with the other hand, often reveals the relation of these trunks. This test will aid also in determining the presence and location of a dilated long saphenous trunk in the thigh of an obese patient.

The Perthes test was designed to give information concerning the patency of the deep veins. This test is performed by placing a tourniquet around the extremity above the varices and observing the condition of the varices as the patient walks. If they become more prominent, the deep veins are obstructed. Such a result from a Perthes test is considered positive. If, however, the varices collapse or become less prominent, the deep veins are patent and the result of the test is negative. Sometimes two tourniquets, one above and one below the varices, give added information. Tourniquets may be placed at different levels along the extremity if necessary. The latter procedure, which is often more efficacious than the simple Perthes test, is called the segmental Perthes test.

The Trendelenburg test aids in locating the incompetent valves. It is performed by elevating the extremity until the varices collapse and then observing the rapidity of filling when the patient stands with a tourniquet

constricting the upper end of the long saphenous vein. The rapidity of filling when the obstructing tourniquet is suddenly removed is also noted. If the varices remain empty or fill slowly with the tourniquet in place and then fill rapidly when the tourniquet is removed, the varicose condition is due to incompetence of the valves in the long saphenous vein. The aforementioned results are classified as singularly positive and include groups 2 and 7.

If the varices fill rapidly with the tourniquet still in place, there is also incompetence of the valves in the communicating veins of the thigh or leg. If additional bulging of the veins is observed when the tourniquet is removed, the valves at the junction of the saphenous with the deep vein are also incompetent. If no additional bulging is noted when the tourniquet is removed, the incompetent valves are in the communicating veins only. The results are classified as doubly positive whenever the varices fill immediately or in less than thirty seconds with the constricting tourniquet still in place. A doubly positive Trendelenburg reaction therefore is obtained in patients of groups III, IV, V, VI and X.

A negative result from a Trendelenburg test indicates that the varices fill slowly from below whether the tourniquet is still in place or not.[3] In this condition no reflux of blood occurs through the saphenous or communicating veins, because the varicose state is due to incompetence of the venous walls and not to valvular insufficiency. In patients of group XI the result of the Trendelenburg test is negative.

If the valves in both the long and the short saphenous vein are incompetent, the examiner must repeat the Trendelenburg test, using two tourniquets, one being placed around the upper part of the thigh and the other just below the knee to constrict the long and the short saphenous vein respectively. The patients in group IX require the use of two tourniquets.

Incompetence of the valves in the short saphenous vein alone may be diagnosed by applying the tourniquet around the leg, just below the knee. The interpretation of the test is similar to that for the long saphenous vein. A singularly positive result from the Trendelenburg test with the tourniquet below the knee indicates that the varices are related to an incompetent short saphenous vein (group VIII). A doubly positive result with the tourniquet below the knee indicates that the incompetent valves are in the communicating veins of the leg (group X).

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3. The three interpretations of the Trendelenburg test given here are the ones most commonly used. Bernstein defined four possible results: positive, negative, double, and nil (Bernstein, A., in McPheeters, H. O.: Varicose Veins with Special Reference to the Injection Treatment, ed. 2, Philadelphia, F. A. Davis Company, 1930, p. 43). His interpretations, however, are more complicated and less widely used.

The comparative tourniquet[4] test is a refined development of the segmental Perthes test, and it may reveal all the information obtainable by both the Perthes and the Trendelenburg test except the degree of incompetency of the valves. The comparative tourniquet test is performed by observing the size of the varices under five (sometimes six) different conditions: (1) with the patient standing; (2) with the patient walking; (3) with the patient walking with a tourniquet around the upper part of the thigh; (4) with the patient walking with a tourniquet around the middle of the thigh, and (5) with the patient walking with a tourniquet around the lower part of the thigh. Occasionally it will be necessary also to observe the varices with the tourniquet around the leg just below the knee. The interpretation is as follows:

1. The deep veins are patent if the varices diminish when the patient walks with or without the tourniquet in place anywhere along the extremity.

2. The deep veins are not patent if the varices increase in prominence during any or all of the walking procedures.

3. The long saphenous valves are insufficient if the improvement in the varices is the same with the tourniquet around the upper part of the thigh as with the tourniquet around the lower part of the high.

4. The valves of the communicating veins in the thigh are incompetent also if the improvement is greater with the tourniquet around the lower or the middle part of the thigh than with the tourniquet around the upper part of the thigh. The location of the incompetent vein or veins can be determined by comparing the degree of improvement at each of the three levels in the thigh.

5. If the varices do not improve with the tourniquet around the lower part of the thigh, one or more of the following conditions exist: The valves in the short saphenous vein are incompetent, the valves in the communicating veins of the leg are incompetent or the deep veins are not patent. In order to distinguish between these three conditions the tourniquet is placed below the knee, constricting the upper end of the short saphenous vein. If the varices are now observed to collapse on walking, the reflux of blood is coming through incompetent valves in the short saphenous vein. If the communicating veins of the leg are insufficient, the varices will remain the same size as when the patient walked with the tourniquet around the lower part of the thigh. If the deep circulation is not patent, the varices will become more prominent on walking.

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4. Mahorner, H. R., and Ochsner, A. O.: The Modern Treatment of Varicose Veins as Indicated by the Comparative Tourniquet Test, Ann. Surg. **107**:927-950 (June) 1938.

6. If the valves in both the long and the short saphenous vein are incompetent, the varices will not collapse until two tourniquets are used, one being placed around the upper part of the thigh and the other just below the knee.

7. If the varices are due to mere dilatation of the venous walls without valvular incompetence, the degree of collapse will be about the same with or without the tourniquet in place.

The elastic bandage test for patency of the deep veins is performed by applying an elastic bandage from the toes to the upper part of the thigh and having the patient walk for several hours. If the deep veins are obstructed the patient will complain of an aching or cramping pain in the extremity. If no pain develops, the deep circulation is unobstructed. The development of pain is caused by acute passive congestion in the extremity. This test will often be the last resort in differentiating between incompetency of the communicating veins in the leg and obstruction of the deep veins.

DIFFERENTIAL DIAGNOSIS

The conditions to be differentiated from varicose veins include the following: femoral hernia, arteriovenous aneurysm, lymphocele, muscle hernia, thromboangiitis obliterans, peripheral arteriosclerosis, Raynaud's disease, diabetic neuritis, erythema induratum, Morton's disease, pes planus, rheumatic pains in the joints, sciatica, tabes dorsalis, ostitis, periostitis and menopausal arthritis. Varicose veins may be associated with any of these conditions, and the symptoms may be attributed to the varices even though the other condition is actually responsible. It is therefore necessary to secure a thorough history, a complete physical examination and adequate tests of the blood and urine as well as a careful evaluation of the arterial system in all cases in which there are symptoms suggestive of varicose veins.

TREATMENT

The active treatment of varicose veins includes the injection of sclerosing solutions, high ligation of the saphenous trunks, excision of large masses of varices and ligation of the communicating veins. The aforementioned procedures are used singularly or in combination. Varicose ulcers are healed by relatively conservative measures before the more radical procedures are undertaken.

Patients with obstruction of the deep veins with compensatory dilatation of the superficial veins receive no active therapy until the obstruction is removed or disappears. If the obstruction is due to recent or persistent thrombophlebitis, the deep venous channels will not become

sufficiently recanalized to allow treatment in less than one year. In some cases recanalization never occurs.

Patients who have only incompetent valves of the long saphenous vein usually receive complete relief from high ligation of the vein. It is essential that the long saphenous vein be ligated flush with the femoral vein and that all superficial veins entering the saphenous fossa be interrupted. Occasionally a sclerosing solution is injected distally into the long saphenous vein at the time of the ligation. For this group of patients, however, it is preferable to delay injections until two to six weeks postoperatively in order to allow the dilated veins to recede in size as much as possible. Large saccular dilatations along the course of the saphenous trunk are excised at the time of the high ligation.

When incompetency of the valves in the long saphenous and communicating veins of the thigh exists, high ligation of the saphenous and simultaneous ligations of the communicating veins are performed. After the patient becomes ambulatory a sclerosing solution is injected into any residual varices.

If the valves in the long saphenous vein and in the communicating veins of the leg are incompetent, these vessels are ligated flush with the deep veins. In order to secure deep ligation of the communicating veins of the leg the modified Madelung, or flap, operation [5] is indicated. The patients in this group are the ones who most often present brawny edema and intractable ulcers.

If the varices are due to incompetent valves in the communicating veins of the thigh and the valves at the femorosaphenous junction are intact, ligation of the affected communicating veins is indicated, and if small varices persist postoperatively, they are treated by injection after the patient becomes ambulatory.

Patients with secondary dilatation of the short saphenous vein due to back pressure through an anastomotic branch from a varicosed long saphenous trunk are usually relieved by high ligation of the saphenous vein and subsequent injection treatment of persistent varicosities.

A varicose condition of the short saphenous vein alone is treated by injections if the varicosities are small. When the varicosities are large, ligation of the short saphenous vein flush with the popliteal vein is performed. Subsequent injections may also be used for persistent varicosities.

Incompetence of the valves in both saphenous veins is treated by high ligation of both venous trunks.

Incompetent communicating veins of the legs without involvement of the saphenous trunks are treated by ligation of the affected veins flush with the deep veins.

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5. Faxon, H. H.: Present Methods of Treating Varicose Veins, New England J. Med. **216**:327-334 (Feb. 25) 1937. Linton.[2]

Dilatations of the superficial veins without valvular incompetence are treated by injections.

During early pregnancy active therapy is justified. Patients in the third trimester of pregnancy, patients with active or recent phlebitis and patients with serious debilitating diseases are treated conservatively.

The sclerosing injections are always carefully and aseptically administered in order to avoid thrombophlebitis, local abscesses or septicemia. If the sclerosing solutions are injected outside the veins, sloughing and ulceration may occur.

The most serious complication of injection therapy is pulmonary embolism. Two patients have died of emboli at the University Hospitals. Both were kept in bed for ten days after the injections. It is essential that all patients remain ambulatory after the injections to avoid this catastrophe.

Excessive amounts of the sclerosing solutions have caused marked toxic reactions. In 1 of our patients, who received 12 cc. of a 5 per cent solution of sodium morrhuate at one sitting, toxic hepatitis with jaundice and a high fever developed. The deep veins may be thrombosed by massive doses of the sclerosing solutions. Severe allergic reactions with marked collapse or even death of the patient have been reported.[6] Hematuria has been observed to follow large doses of hypertonic solution of sodium chloride.

The fatty acid derivatives have proved to be the safest and most efficacious solutions for injection. Sodium morrhuate is the most widely used. At the University Hospitals the maximum dose for one sitting is 5 cc. of the 5 per cent solution. Other effective fatty acid preparations are monoethanolamine oleate (monolate), sodium ricinoleate, potassium oleate, sodium gynocardate and sylnasol.[7]

Operating room technic is used for the ligation and excision procedures, which carry about a 2 per cent risk of major wound infection and a 0.3 per cent risk of pulmonary embolism.[8] No patient has died after any of the operative procedures at the University Hospitals.

The patient may remain ambulatory after high ligations of the saphenous vein, but great care is always exercised postoperatively to prevent infection of the wounds. Most patients treated by means of multiple ligations or excisions remain in bed until the wounds are suffi-

6. Johnson, G. S.: Recent Advances in the Treatment of Varicose Veins, Surgery **2**:943-965 (Dec.) 1937.

7. Sylnasol (G. D. Searle & Co.), formerly known as sylasol, is a 5 per cent solution of the sodium salts of certain of the fatty acids of the oil extracted from a seed of the psyllium group.

8. Faxon, H. H., and Barrow, D. W.: The End Results of High Ligation and Injection in the Treatment of Varicose Veins, Surgery **3**:518-527 (April) 1938.

ciently healed for the skin sutures to be removed. After the skin sutures are removed, Unna's paste boots [8a] are applied. These are worn for seven to twenty-one days.

Recurrence of the varicose veins in less than one year occurs in from 10 to 25 per cent of even the most favorably treated patients.[9] Our experience confirms this. Three factors account for most of the recurrences in the patients treated at the University Hospitals: (1) failure to ligate all the important "blow-out" vessels flush with the deep veins; (2) failure to excise large saccular masses of veins, and (3) failure to complete the treatment by injections into all the varices which persist postoperatively.

All patients are encouraged to return for periodic examinations and for treatment of the varices that may persist or recur after the primary therapy.

SUMMARY

A classification of varicose veins is presented for use in treating this disease.

A résumé of the various diagnostic tests for varicose veins is given. The tests are interpreted with reference to the possible variations in venous incompetency.

The differential diagnosis of varicose veins is emphasized.

The selection of patients and the indicated therapeutic procedures are discussed.

The rules for avoiding the more important complications are emphasized.

8a. The formula for Unna's paste is as follows: gelatin, 150 Gm.; glycerin, 400 Gm.; water, 350 Gm., and zinc oxide, 100 Gm. The first three ingredients are melted together, and zinc oxide, previously rubbed with a portion of the glycerin, is added. The boots are made by soaking loosely rolled 3 inch (7.5 cm.) cotton bandage in the melted paste. The extremity is bandaged from the base of the toes to the middle of the thigh. Five to seven layers of the gauze will give satisfactory support. After the boot has dried for twenty to thirty minutes the surface is powdered with talcum.

9. Ferguson, L. K.: Ligation of Varicose Veins: Ambulatory Treatment Preliminary to Sclerosing Injections, Ann. Surg. **102**:304-314 (Aug.) 1935. McPheeters, H. O.: The Present Status of the Management of Varicose Veins, Surg., Gynec. & Obst. **67**:494-498 (Nov.) 1938. de Takáts, G.: Varicose Veins, in Christopher, F. A.: A Textbook of Surgery, Philadelphia, W. B. Saunders Company, 1936, p. 168. Johnson.[6] Faxon and Barrow.[8]

NERVE ACTION POTENTIALS IN EXPERIMENTAL TRAUMATIC SHOCK

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The role of the nervous system in the production of shock in the experimental animal has been emphasized by Slome and O'Shaughnessy,[1] who stated:[1a] "The initial depressor effect of trauma is due to fluid loss; the significant secondary decline to shock is caused by the continued and continuous discharge of nervous impulses from the traumatized area. The nervous factor operating alone can cause death." These experiments have been discussed by Blalock and Cressman.[2]

Direct evidence for a nervous factor was adduced by O'Shaughnessy and Slome[1a, c] by comparing records of the action currents in the nerves to a traumatized limb before and after trauma with those of the action currents in the nerves to the untraumatized control limb of the same animal. They stated:[1a]

> No abnormal impulses are recognizable for three quarters of an hour to one hour after trauma; after this time an almost continuous barrage of impulses is rapidly developed. These can be shown to be centripetal afferent impulses by ligaturing, sectioning or novocainizing the nerves peripheral to the electrodes. The absence of any impulses for a period after trauma, and their appearance after this time and persistence till death of the animal, accords accurately with the gradual decline of blood pressure which sets in at this time.

Only two illustrative records of such impulses are shown, one in each article,[1a, c] without a description of methods used to record the nerve action potentials. However, some conclusion may be drawn regarding

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1. (*a*) Slome, D., and O'Shaughnessy, L.: The Nervous Factor in Traumatic Shock, Brit. J. Surg. **25**:900, 1938. (*b*) O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock, ibid. **22**:3, 1935. (*c*) Slome, D.: Traumatic Shock, Proc. Roy. Soc. Med. **28**:73, 1935.

2. Blalock, A., and Cressman, R.: Experimental Traumatic Shock: Further Studies with Particular Reference to the Role of the Nervous System, Surg., Gynec. & Obst. **68**:278, 1939.

the amount of amplification employed by comparing the resting discharge with the discharge produced in response to tactile stimulation.[1c]

PURPOSE OF THIS STUDY

The experiments reported here were undertaken in an attempt to verify the existence of a barrage of impulses in experimental traumatic shock as reported by O'Shaughnessy and Slome and to determine, if possible, the origin of such a barrage and whether it is a causative factor in shock or is related to the low blood pressure, vasoconstriction and other changes which are a part of shock.

METHOD

Action potentials of the nerve studied were amplified through a resistance-coupled amplifier operated by alternating current, and connected to a dynamic speaker type of oscillograph. The deflections were recorded on moving bromide paper. Amplification through this system was adjusted to give a deflection of about 1 cm. from the base line in response to light stroking of the skin when the saphenous nerve was used or to muscle stretch by flexion at the knee in the case of muscular branches of the femoral nerve. The femoral nerve was exposed below the inguinal ligament, and records were made from the isolated saphenous nerve or from a portion of the muscular branches to the quadriceps muscle. Silver electrodes with an interelectrode distance of 5 mm. were used; the nerve was kept moist with saline solution on cotton pledgets in the interval between recordings. In nearly all cases the intact nerves were used, but occasionally nerves were sectioned proximal to the electrodes to assure elimination of centrifugal action potentials.

Cats weighing 1,700 to 3,500 Gm. were used in all experiments. They were anesthetized with chloralose (a preparation of chloral hydrate and dextrose), 80 mg. per kilogram of body weight, given intravenously in most of the experiments. In a few cases pentobarbital sodium, 25 mg. per kilogram, was used. One carotid artery was exposed for the intermittent recording of blood pressure by a large needle connected to a mercury manometer. Continuous recording with a kymograph was unsatisfactory because of clotting and the resultant loss of blood in washing out the system.

After exposure of the nerves and the carotid artery in the anesthetized animal, a control tracing was taken from the nerve of each hind leg to obtain the response to touch or stretch and the base line of spontaneous electrical activity in the nerve before trauma. One thigh was then traumatized as described by O'Shaughnessy and Slome,[1a] by twenty blows with an iron bar, the femur being broken in about half the cases. Records were taken from the traumatized and from the control side within five minutes and at intervals of fifteen to thirty minutes thereafter to demonstrate both the spontaneous electrical activity and the sensory response of the nerves in both legs. In animals in which the femur was broken it was not possible to record the stretch response in the muscular branch after trauma.

Loss of fluid into the traumatized extremity was measured by the method described by Blalock,[3] that is, comparison of the weight of the traumatized and untraumatized legs and expressing the increase in weight of the traumatized leg as per cent of total body weight.

CONTROL RESULTS

Records were made of the action currents in the saphenous nerve of one leg and a muscular division of the femoral nerve in the opposite leg for periods of six and one-half to nine hours after the administration of chloralose to 4 cats. Records from the muscular division in 1 experiment showed a slight increase in spontaneous impulses for a short period four hours after the start of the experiment. In the other experiments there was no alteration in spontaneous activity or sensory response in the saphenous or muscular divisions.

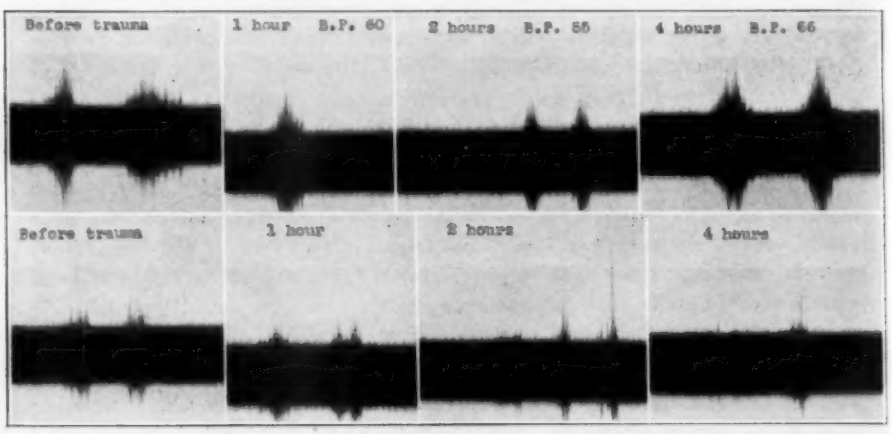

Fig. 1.—Record of nervous activity in the saphenous nerves of cats anesthetized with chloralose and subjected to trauma. The record for the traumatized extremity before trauma and one, two and four hours after trauma is shown at the top of the figure. The response to stroking of the thigh is shown in each record. Note the level of resting activities between responses. The record for the control (untraumatized) extremity at the same intervals is shown at the bottom of the figure.

EXPERIMENTAL RESULTS

Group 1 (saphenous nerves; chloralose anesthesia; trauma to thigh).—In the 6 cats in this group of experiments, the fluid loss into the traumatized leg was from 1.2 to 3 per cent of the body weight, with the average 2.4 per cent. In 4 of the experiments there was no change in electrical activity in the nerves after trauma (fig. 1), while in 2, increases were seen. In 1 this occurred one and one-quarter hours after trauma, when the blood pressure had fallen to 100 mm.

3. Blalock, A.: Experimental Shock: Cause of Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959 (June) 1930.

of mercury. The increase was rather slight and was equal on the traumatized and on the control side. In the other there was an increase on the control side only four hours after trauma, when the blood pressure was 65 mm. of mercury.

GROUP 2 (muscular branch of femoral nerve; chloralose anesthesia; trauma to thigh).—In the 13 cats in this group the loss of fluid into the traumatized leg varied from 1.9 to 3.2 per cent, averaging 2.4 per cent, of the body weight. Six cats showed no change in nerve activity; 7 showed slight to marked increase in activity, both in spontaneous discharges and in response to stretch. In 2 of these experiments the increase was greater on the traumatized side; in 1 it was greater on the nontraumatized side (fig. 2) and in the remaining 4 it was equal on the two sides (fig. 3).

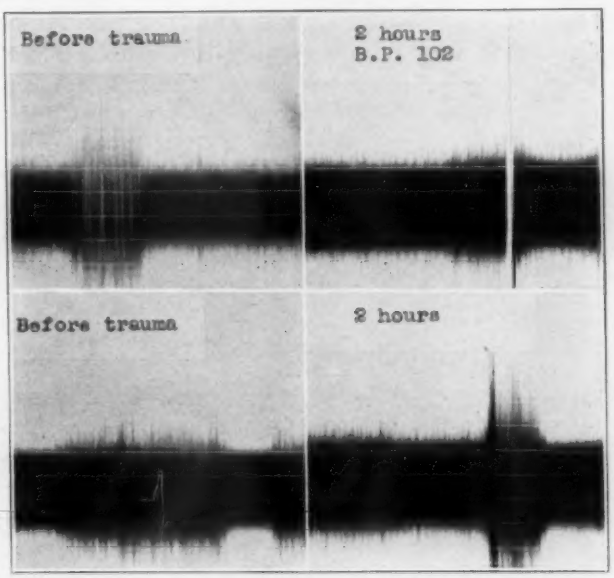

Fig. 2.—Record of nervous activity in muscular branches of the femoral nerves of cats anesthetized with chloralose and subjected to trauma. The record for the traumatized extremity before trauma and two hours after trauma is shown at the top of the figure. Response to stretch is shown in each record, as well as resting activity. The record for the control extremity is shown at the bottom of the figure.

Of the 7 experiments in which there was any increase in the level of electrical activity in the nerves following trauma, in 3 this change began within five minutes after trauma and continued for the duration of the experiment. In 2 heightened activity was first observed two hours after trauma, and in the remaining 2, three hours after trauma. At the time the increased activity was first noted, the mean blood pressure varied from 88 to 125 mm. of mercury.

Of 3 experiments in which pentobarbital sodium was the anesthetic, there was an equal increase in activity in the nerves of both legs in 1, beginning two hours after trauma, when the mean blood pressure was 120 mm. There was an increase

in activity in the nerve in the control leg in 1, beginning one hour after trauma, at which time the mean blood pressure was 74 mm. of mercury, and in the remaining instance there was no change aside from impulses which immediately followed the trauma and which were accompanied by twitching of the muscles.

GROUP 3 (saphenous nerve and muscular branches of femoral nerve; chloralose anesthesia; shock by hemorrhage).—To determine if possible whether the increase in spontaneous nerve impulses seen in both traumatized and nontraumatized extremities was related to the anoxemia succeeding low blood pressure and peripheral vasoconstriction, shock was induced in anesthetized cats by removal of blood from the carotid artery in 6 experiments. To reduce the blood pressure below 80 mm. of mercury, blood in the amount of 2.5 to 3.5 per cent of the body weight was gradually removed in one and a half to three hours. Loss of this amount of blood leads to death within three to six hours, often soon after the blood pressure

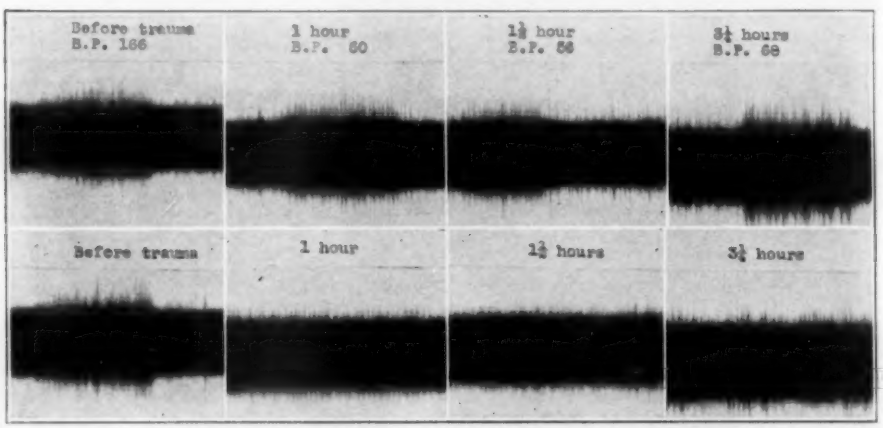

Fig. 3.—Record of nervous activity in muscular branches of the femoral nerves of cats anesthetized with chloralose and subjected to trauma. The record for a nontraumatized extremity before trauma and one, one and one-half and three and one-quarter hours after trauma is shown at the top of the figure. The stretch response as well as the resting discharge is seen in each record. The record for the traumatized extremity at the same intervals is shown at the bottom of the figure. The stretch response is seen only in the first record. The increase in resting activity is about equal on the two sides.

reaches shock level. In 4 cats no change in nerve activity occurred in either the saphenous or the muscular branch. In 1 there was a slight transient increase when the blood pressure was 80 mm. of mercury, and in the remaining one there was a marked increase in spontaneous activity and response to touch and stretch after the blood pressure had been reduced to shock level.

GROUP 4 (trauma to isolated muscle).—In 3 experiments a single muscle of the quadriceps group of the thigh, with its vascular and nerve supply, was isolated to record action potential changes when this single muscle was traumatized. Diffi-

culty in maintaining conduction in the nerve after trauma to the muscle caused abandonment of this line of attack.

GROUP 5 (anemic limb).—O'Shaughnessy and Slome [1a] in cross circulation experiments rendered a leg anemic, believing such a leg to be anesthetic. To determine whether such anemia would result in increased or absent nerve action currents, anemic limb preparations were made in 4 cats by ligating the aorta, the iliolumbar artery, the middle sacral artery, the external iliac artery, the profunda femoris artery and the femoral artery and its branches in the groin together with the corresponding veins. In 1 instance no responses were obtained in the nerves of either the anemic or the control limb; in another there was no change in the action potentials, the femoral nerve in the anemic limb responding to stretch for three and a half hours, after which it gradually failed, while in the 2 remaining experiments increases in nervous activity were seen. In 1 case the nerve in the anemic leg and in the other that in the control leg showed the greater increase. Continued electrical activity in response to stretch for three and a half and six and a third hours respectively in the nerve to the anemic limb in 2 experiments would indicate that the leg was probably not anesthetic.

COMMENT

That the impulses described by O'Shaughnessy and Slome or those seen in the experiments reported here can be stated to be nociceptive seems extremely doubtful. Fulton [4] described as nociceptive those impulses arising from the free nerve endings which mediate pain in response to a noxious agent. From our knowledge of fiber size and the relative size of the action potentials associated with pain compared with those of touch or proprioception, as pointed out by Erlanger and Gasser,[5] it is unlikely that pain impulses could have been recorded for the intact animal by the methods of O'Shaughnessy and Slome or by our own methods. We have attempted to record impulses arising in response to pain by the application of a hot rod to the cat's leg. This produces only a short burst of impulses in the nerve, corresponding to touch, followed by a return to the previous level, without any recognizable impulses as evidence of the pain following such a burn. A recent investigation by Zotterman [6] has demonstrated in thin preparations from the saphenous nerve the electrical response in the nerve following pinprick or burning, demonstrating the low amplitude of the electrical response as compared with action currents resulting from touch. If

4. Fulton, J. F.: Physiology of the Nervous System, London, Oxford University Press, 1938.

5. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937.

6. Zotterman, Y.: Touch, Pain and Tickling: An Electrophysiological Investigation in Cutaneous Nerves, J. Physiol. **95**:1, 1939.

pain impulses were recorded, one would immediately record a barrage of impulses in the nerve to the traumatized limb in experimental traumatic shock which would continue throughout the experiment instead of appearing only after three quarters of an hour to an hour after the trauma, as O'Shaughnessy and Slome have found. The possibility remains that other types of impulses, i. e., other than pain, are nociceptive. Electrical responses related to impulses in the sympathetic nervous system are even smaller than those related to pain. There is no good evidence that impulses arising in the proprioceptive or the tactile nerve endings are nociceptive.

Our experiments fail to confirm the regular presence of a barrage of impulses in the nerves of the traumatized limb, either in the saphenous or in the muscular branch. Equal increases in nervous activity have been recorded for both the traumatized and the control legs, as well as increases in the activity of the nerves to the traumatized leg and occasionally a greater increase in that of the nerves of the control leg. This may indicate that the increased impulses accompany shock rather than that they are its cause. Further suggestive evidence for this view is seen in the increased nervous activity occurring in 2 of the experiments in which shock was produced by hemorrhage alone and in anemic limb preparations for which increased nerve action potentials were recorded. These observations are in accord with those of Thompson and Kimball [7] and of Matthews,[8] who noted that interference with blood supply to nerve endings lowers their threshold and initiates an increased spontaneous discharge of nervous impulses. Shock produced by trauma to a limb or hemorrhage, and the preparation of an anemic limb are associated with tissue anoxia, either by peripheral vasoconstriction or by direct interference with the blood supply, and under these conditions spontaneous nerve impulses, as well as increased response to touch or stretch, may occur.

The effect of drying of the nerve, as has been pointed out by Zotterman,[6] is to increase the signal noise ratio. This makes it difficult or impossible to compare successive records, even though the nerve is kept moistened. Varying levels of anesthesia and alteration in muscle tone in the anesthetized intact animal serve further to confuse the interpretation of recorded nervous impulses. Increases that have been observed are afferent impulses, as can be demonstrated by section of the nerves.

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7. Thompson, I. M., and Kimball, H. S.: Effect of Local Ischemia upon Human Nerve Fibers in Vivo, Proc. Soc. Exper. Biol. & Med. **34**:601, 1936.

8. Matthews, B. H. C.: Nerve Endings in Mammalian Muscle, J. Physiol. **78**: 1, 1933.

It is suggested that when increased nerve action potentials are recorded in the nerves to the limb in experimental traumatic shock, they may be associated with an altered metabolic state of the nerve endings resulting from the vascular changes occurring in shock and that such impulses probably arise in tactile or proprioceptive nerve endings, not in the free nerve endings for pain, and are therefore not nociceptive.

SUMMARY

In shock produced by trauma to the limb of an anesthetized animal, no consistent barrage of nerve impulses has been observed in the nerves of the traumatized limb.

Increased nerve impulses have been recorded in nerves of untraumatized as well as traumatized extremities.

The possible origin of such impulses is discussed.

SURGICAL EXCISION OF MATERIAL FOR BIOPSY IN THE LYMPHOMATOUS DISEASES

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For many years the primary lymphadenopathies, such as Hodgkin's disease, lymphosarcoma, Brill-Symmer's lymphadenopathy and the pseudoleukemic lymphomas, were diagnosed and differentiated by means of clinical signs and symptoms correlated with the history and the laboratory findings. Diagnostic tests have been devised, but none has received widespread use or acclaim, owing to variabilities and inconsistencies in interpretations and in technic. In the Memorial Hospital, histologic examination of material obtained by surgical excision is regarded as the most reliable guide for an accurate diagnosis in this group of diseases. This report is an attempt to clarify the confusion regarding certain aspects of excision, aspiration, punch and removal of a wedge as applied to biopsy in cases of the lymphomas.

In the ordinary routine of medical practice, the opportunities for excising a diseased lymph node are relatively rare. Patients who have diffuse lymphadenopathies are generally afflicted with Hodgkin's disease, lymphosarcoma, one of the leukemias or tuberculosis; more rarely, with metastatic carcinoma, sarcoma or syphilis. At the Memorial Hospital the lymphomatous diseases are concentrated in one clinic, and there is an opportunity to examine a great variety of clinical material. In addition to the new patients that present themselves for diagnosis, there is a larger group of referred patients whose cases illustrate the confusion regarding methods of obtaining material for histologic examination.

In former years the lymphomatous diseases have been the special problem of the internist. Today the proper management of the patient requires the cooperation of the internist, the surgeon, the pathologist and the roentgenologist. Present day therapy is based on (1) the histologic diagnosis, (2) the extent of the disease, (3) the response to radiation therapy, (4) the age of the patient and (5) the known clinical course of the disease in question.

Owing to the protean character of the early lymphomas, a diagnosis is often difficult to establish even with adequate material for biopsy.

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases, the Lymphoma Clinic of Dr. Lloyd F. Craver.

Clinically the patient may present only a moderate degree of local or generalized lymphadenopathy. Diagnostic tests, such as that of Gordon,[1] have been advocated for the purpose of obtaining a specific reaction for the early stages of Hodgkin's disease. In general, such tests for specific reactions are still in the experimental stages and have failed to replace histologic examination of the excised lymph node. Additional confirmation may prove the value of biologic tests in cases in which examination of material obtained by surgical excision is inconclusive.

There are advocates of "punch biopsy" or "aspiration biopsy" as methods for diagnosing diseases of the lymph nodes. Experience at the Memorial Hospital has shown that examination of material obtained by aspiration from a suspected primary or secondary lymphoma is not an entirely reliable diagnostic procedure. Study of aspirated material as described by Martin and Ellis [2] has proved to be a valuable aid in the diagnosis of primary and metastatic cancer. The advantages and disadvantages of this method have been described by Martin and Stewart.[3] The pathologist can recognize carcinoma and sarcoma from a smear of material aspirated from a lymph node; however, in the case of the lymphomas the smear may only offer highly suggestive characteristics. A differential diagnosis made from smeared material obtained from a lymphoma is difficult and often unreliable. The same difficulty applies to biopsy material obtained by punch in this particular group of diseases.

Stewart,[4] who has had wide experience in the interpretation of biopsy material obtained by needle aspiration, advocates the method only in cases of doubtful enlargement of the lymph nodes, in order to rule out the presence of metastatic tumor. He stated that when the primary lymphadenopathies, i. e., Hodgkin's disease, lymphosarcoma, pseudoleukemic lymphoma, Brill-Symmer's lymphoma and the like, are suspected from clinical examination and when metastatic tumor has been ruled out, it is preferable to obtain material for biopsy by surgical methods, as fixed smears, in his opinion, are unreliable in the diagnosis of the lymphomas.

Forkner [5] reported a method of puncturing primary lesions of the lymph nodes in which he identified the material obtained by means of

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1. Gordon, M. H., in Horder, T., and others: Rose Research on Lymphoadenoma, Bristol, John Wright & Sons, Ltd., 1932, pp. 14-48.

2. Martin, H. E., and Ellis, E. G.: Aspiration Biopsy, Surg., Gynec. & Obst. **59**:578, 1934.

3. Martin, H. E., and Stewart, F. W.: The Advantages and Limitations of Aspiration Biopsy, Am. J. Roentgenol. **35**:245, 1936.

4. Stewart, F. W.: The Diagnosis of Tumors by Aspiration, Am. J. Path. (supp.) **9**:801, 1933.

5. Forkner, C. E.: Material from Lymph Nodes of Man: I. Method to Obtain Material by Puncture of Lymph Nodes for Study with Supravital and Fixed Stains, Arch. Int. Med. **40**:532 (Oct.) 1927; II. Studies on Living and Fixed Cells Withdrawn from Lymph Nodes of Man, ibid. **40**:647 (Nov.) 1927.

supravitally stained preparations. Pavlowsky [6] of Buenos Aires, Argentina, has written a monograph on the diagnosis of diseases of the lymph nodes. He examined material obtained by puncturing the lymph node with a needle.

In 1923, surgical excision of an involved lymph node was introduced in the lymphoma clinic of the Memorial Hospital, and it has become a routine procedure in cases in which the diagnosis is unconfirmed. In the group of atypical cases in which the results of the initial biopsy is inconclusive, repeated biopsies at a later stage of the disease generally establish the diagnosis. Many of the patients admitted for therapy have had biopsies performed elsewhere before applying to the clinic. Referred patients are required to obtain a slide of the original biopsy section for a review before treatment is outlined.

REPORT OF CASES

CASE 1.—This case illustrates the difficulty occasionally encountered in diagnosing the atypical lymphomas. During three and one-half years three biopsies of material obtained by excision and 1 of material obtained by aspiration were performed before a definite histologic diagnosis was finally established (surgically excised material).

A white man aged 45 was first examined in another hospital because of a tumor in the right groin. At that time he stated that a similar mass had appeared twelve years previously. This mass disappeared after four or five months and remained absent until three years prior to his admission to this hospital. He stated that the mass had slowly enlarged during the three years of its recurrence. He was admitted to the Lincoln Hospital to the service of Dr. Bradley L. Coley, and on Jan. 6. 1934, a mass measuring 7 by 4 by 3.5 cm. was excised from the right groin. A slide of the tissue was submitted to Dr. Fred W. Stewart of the Memorial Hospital, who reported a diagnosis of inflammatory lymphoma.

On January 26 the slides were reviewed again, by Dr. James Ewing and Dr. Stewart, who reported, "Not a lymphosarcoma. This might be Hodgkin's but is not diagnosable as such. Syphilis must be ruled out and also granuloma inguinale. We cannot make a diagnosis."

Tissue was aspirated from a node in the region of the parotid gland on Nov. 2, 1936. Dr. Stewart reported: "Some type of lymphogranulomatosis with salivary gland infiltration." On November 18 a node measuring 4 by 3 by 1.5 cm. was excised from the opposite (left) groin. Histologic study showed "atrophied lymphoid tissue with fibrosis and some phagocytosed pigment."

On March 5, 1937, a node measuring 4 by 3 by 2 cm. was excised from the left femoral triangle. Dr. Stewart reported: "Giant follicular lymphosarcoma, presumably Brill's type, but atypical and malignant looking."

Thus, after three years and three months a definite histologic diagnosis was obtained. The early failures were due not to lack of adequate material or to faulty interpretation but rather to the nature of the disease.

CASE 2.—This case illustrates again the confusion in diagnosis because of features that may be regarded as interrelated in the lymphomatous diseases.

6. Pavlowsky, A.: La puncion ganglionar: Su contribucion al diagnostico clinico quirurgico de las afecciones ganglionares, Buenos Aires, A. Lopez, 1934.

A white man aged 68 was admitted to the Memorial Hospital with a clinical diagnosis of either Hodgkin's disease or lymphosarcoma of the right side of the neck. There was marked involvement of the right side of the neck, with moderate generalized lymphadenopathy involving the axillas and the groins. There was no palpable enlargement of the liver or the spleen. Roentgenograms of the chest disclosed a mediastinal mass. The history of lymphadenopathy was of one year's duration. There was no history of significant pruritus or fever. Previous studies of the blood had shown values consistent with a diagnosis of lymphatic leukemia. Studies of the blood on admission showed: hemoglobin, 85 per cent; red blood cells, 4,224,000 per cubic millimeter; white blood cells, 13,900 per cubic millimeter, with 39 polymorphonuclears, 57 small lymphocytes, 2 transitional cells and 2 eosinophils. A cervical lymph node was surgically excised (Feb. 18, 1936), and Dr. Ewing reported, "Diffuse lymphoma. Structure suggests leukemic hyperplasia." This seemed to confirm the impression of chronic lymphatic leukemia previously suggested by the blood count, despite the clinical impression of Hodgkin's disease or possibly lymphosarcoma.

The patient was treated by means of the 4 Gm. radium element pack applied to the right side of the neck. There was marked regression of the disease. However, the patient refused to complete the therapy outlined and died in another institution on Sept. 17, 1937. Autopsy disclosed chronic myocarditis, terminal bronchopneumonia and pulmonary edema. Microscopic sections of the lymph nodes obtained at autopsy were referred to the Memorial Hospital and were reviewed by Drs. Ewing and Stewart. Histologic study showed classic Hodgkin's granuloma. A review of the previous (antemortem) biopsy, by Dr. Stewart, was reported as follows: "I would surely have called it a leukemic node."

In this case, the autopsy finally confirmed the original clinical impression of Hodgkin's disease.

Wallhauser,[7] Warthin,[8] Craver [9] and others have mentioned the close interrelation of the lymphomatous diseases. Craver reported a number of cases that illustrate the uncertainty of diagnosis by biopsy in these conditions and suggested an interrelation between leukemia, Hodgkin's disease and lymphosarcoma. He reported a case in which the condition had run a leukopenic course for three years and in which biopsy had shown giant follicular lymphoma. Autopsy revealed lymphatic leukemia with infiltration of the liver, spleen, stomach, kidneys, adrenals and all the superficial and deep nodes. Ultimately, after microscopic studies, the condition in this case was diagnosed as leukosarcoma. Another case reported by Craver was one of lymphosarcoma in which the diagnosis was proved by biopsy, and in which generalized symptoms developed. Autopsy revealed generalized leukemic changes.

In the atypical lymphomas the diagnosis should not be established on questionable histologic features but should be substantiated by

7. Wallhauser, A.: Hodgkin's Disease, Arch. Path. **16**:522 (Oct.); 672 (Nov.) 1933.

8. Warthin, A. S.: Neoplastic Relationships of Hodgkin's Disease, Ann. Surg. **93**:153, 1931.

9. Craver, L. F.: Clinical Manifestations and Treatment of Leukemia, Am. J. Cancer **26**:124, 1936.

definite confirmatory proof. Biopsy material obtained at intervals during the course of the disease is especially desirable in the presence of conditions which tend to run a pseudoleukemic course.

SELECTION OF BIOPSY MATERIAL

It is important in a given case to select a typically diseased lymph node for excision. One must attempt to distinguish diseased or involved nodes from simple regional lymphadenopathies associated with infected teeth or diseased tonsils and from nodes that may be considered within normal limits.

It is undesirable to excise an irradiated lymph node for the purpose of establishing a histologic diagnosis. If a biopsy has not been performed, an attempt should be made to find a suitable untreated node which shows evidence of being involved in the disease process. If no such node is available, the biopsy should be deferred until new or suitable nodes appear. Treatment should be started, however, on the basis of available clinical data. In patients who have been irradiated the node selected for excision should be situated outside the field of the previous radiation therapy.

Occasionally, small, discrete involved nodes will be found adjacent to the site of a bulky conglomerate mass. These nodes are generally freely movable and easily excised; they are the nodes of choice. A node smaller than 1 cm. in diameter may not prove typical of the disease. Small, friable nodes are easily traumatized and destroyed in removal. The node of choice measures approximately 1.5 to 2 cm. in diameter, is freely movable and is not adjacent to important nerves or vessels.

SITE OF ELECTION

The neck is the site of election for surgical excision of material for biopsy in the widely disseminated lymphadenopathies. The advantages of the cervical region are: (1) ease of excision, (2) freedom from irritation and wound infection and (3) ease of postoperative dressings and care.

The most superficial of the lymph nodes that appear involved should be selected for removal. Nodes situated along the lateral border of the trapezius muscle should be avoided. Capable surgeons have injured the spinal accessory nerve during the dissection of a lymph node located along the border of this muscle. It is important to remember that the axillary and inguinal nodes are more intimately associated with the larger lymphatic vessels and that dissections in the axilla and in the groin increase the hazards of postoperative drainage of lymph. These areas should be avoided if possible. Hair follicles and sweat glands predispose to infection. In the event that the disease is limited to the axillas or to the groins, special care should be used in aseptic technic.

ATTITUDE OF THE SURGEON

Surgical excision of a diseased lymph node is regarded by some surgeons as an operation of minor importance. Such a procedure is generally delegated to a junior intern, often without advice. It is not my purpose to dramatize excision of material for biopsy as a technical procedure. However, the casual order, "excise node for biopsy specimen," should be condemned. The attending surgeon should stress (1) the importance of carefully selecting typical material for the benefit of the pathologist and (2) the importance of approaching the problem from the point of view of the histologic, clinical and cosmetic results.

Often such minor operations are performed hurriedly. Incisions are made much larger than necessary, frequently in violation of all rules

Fig. 1.—*A*, injudicious incision for removal of tissue for biopsy. *B*, injudicious exploratory incision.

of plastic and cosmetic surgery (fig. 1). Undesirable postoperative complications, such as hematoma, infection and lymph drainage, are the telltale signs of injudicious surgical procedures.

Craver [10] recalled 1 patient in whom the physician accidentally severed the spinal accessory nerve during the removal of a cervical lymph node. Ewing, in a personal communication, cited an almost fatal hemorrhage which followed the removal of a lymph node. The surgeon had performed a hurried operation and had allowed the patient to return home, where she became exsanguinated. I have seen 2 patients in whom persistent drainage of lymph followed the use of plain catgut ligatures in the region of the groins. In both of these patients profuse drainage of lymph persisted for a week to ten days despite pressure

10. Craver, L. F.: Personal communication to the author.

and attempts to control the drainage without opening the wound. In the admitting department of the Memorial Hospital it is a rather common experience to see patients referred for diagnosis and treatment who exhibit large tumors that are infected and fungating because of injudicious exploratory incisions (fig. 2). In general, these patients have had one or more incisions made by a family physician under the false impression that the swelling was due to localized inflammation. All enlargements of lymph nodes and lymph node–bearing areas should receive cautious consideration, and in no instance should a tumor or a swelling be indiscriminately incised. Frequently wounds have been

Fig. 2.—Incorrect technic.

erroneously packed wide open or drained. In such instances the diagnosis of neoplasm becomes obvious when the growth fungates through the open wound. Infection and fungation add to the miseries of both the patient and the surgeon. Excision of tissue for biopsy belongs to the field of cancer surgery, and in this type of procedure caution and thoroughness are of more importance than haste.

TECHNICAL SUGGESTIONS

To remove a lymph node intact through a small incision requires time and a certain degree of patience and dexterity. There are, of course, theoretic objections to a cramped technic. For example: 1. Unnecessary trauma may result from an operation performed through an inadequate surgical exposure. 2. Large incisions are said to heal as

quickly as small ones. 3. A cramped technic is unnecessary and makes a time-consuming operation of a simple procedure. Certain of these criticisms are well taken; however, the general standard of results seems to justify a more cautious attitude regarding excision of material for biopsy, with particular reference to the lymphomatous diseases.

No attempt should be made to excise a deeply situated node through a tiny incision. Particularly is this true in dealing with axillary or femoral nodes in an obese patient. If a node in the axilla or the groin is the only available source of biopsy material, one should have adequate surgical exposure. The larger dilated lymphatics should be doubly ligated with nonabsorbable suture material; they occasionally require the additional precaution of a suture ligature. Ordinary plain catgut ligatures may become soft and cause distressing lymph drainage. A poorly ligated lymph vessel will drain for days unless steps are taken to control it. The condition is annoying to the patient and requires frequent changes in the dressing. The moisture makes the application of a tight compression bandage (groin or axilla) a difficult problem. In large incisions this complication predisposes to infection, wound separation and fungation. Once a wound starts draining lymph, a carefully placed secondary combined skin and subcutaneous suture of the vertical mattress or so-called on end mattress type generally controls the drainage and holds the edges of the wound intact. More or less lymphedema results. Careful silk technic in ligating the major lymph vessels prevents postoperative lymph drainage. The theoretic objection to the use of nonabsorbale ligatures as regards infection and sinus formation presupposes a rigid aseptic surgical technic.

Points of technical value are: 1. A few cubic centimeters of 0.5 per cent or 1 per cent solution of procaine hydrochloride should be injected along the deeper structures before the blood and lymph vessels associated with the node are clamped. The ordinary infiltration sufficient to anesthetize the skin may not render the deeper vessels and nerves insensitive to the trauma of division and ligation. 2. The skin sutures should be left in situ longer than usual if radiation therapy is started within a day after operation. Early removal of skin sutures plus early irradiation favors separation of the cutaneous margins, poor healing and the possibility of infection and tumor fungation (fig. 2). There are no objections to the early application of roentgen rays if the cutaneous incision is small and if the sutures are left in situ until healing is firm (fig. 3).

Occasionally lymphomas appear as solitary tumors in the cervical, axillary, inguinal or femoral regions and may be fixed and not suitable for total removal (fig. 4). Careful examination may not reveal a suitable node for excision. In such masses a punch may enable one to

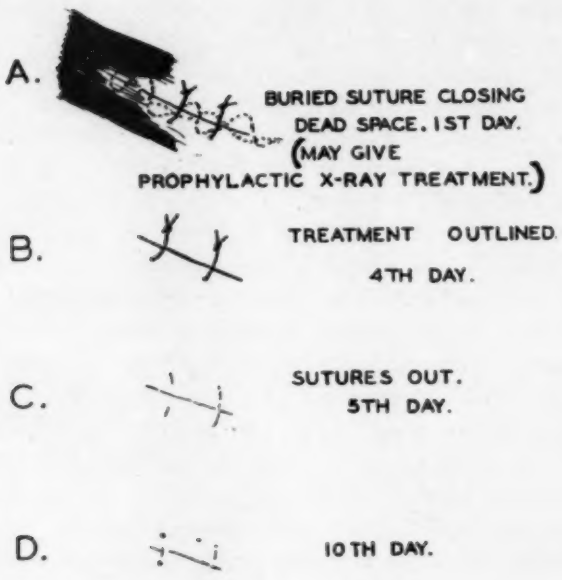

Fig. 3.—Correct technic.

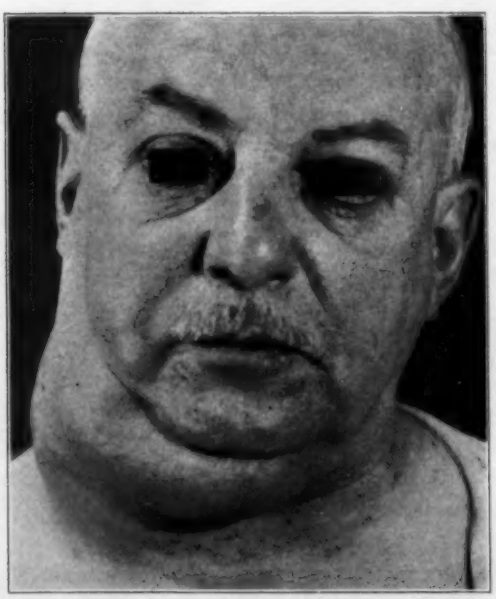

Fig. 4.—Diffuse tumor. In the presence of such a growth material for biopsy may be obtained by aspiration or by removal of a wedge of tissue.

obtain sufficient material for a routine paraffin section. As has been mentioned, the smear method of examining tissue is not advisable in cases of lymphoma, but if sufficient material is obtained a quick smear may show highly suggestive histologic features of the disease. In such selected cases radiation therapy may be instituted as a therapeutic test. However, an attempt to obtain tissue for a routine section should be made at some future date. If physical examination does not reveal a suitable node for excision and if the tissue obtained by punch definitely fails to establish the histologic diagnosis, one must resort to the undesirable "wedge biopsy." It is very important, especially in the presence of a solitary mass in the neck, to visualize carefully the oral cavity, the nasopharynx, the hypopharynx and the larynx for evidence of a primary tumor.

In excision of a wedge also a small cutaneous incision is desirable. The incision should be made at the margin of the tumor rather than directly over the mass. The exposure should be adequate to insure safe removal of a typical wedge of tumor tissue. Palpation through the wound is not a reliable guide to tumor tissue. The glistening surface of the tumor should be visualized and the tumor mass identified by direct vision. Attempts at blind removal of a wedge of suitable material by feel should be avoided. A wedge of tissue may be obtained and a defect palpated in the remaining mass, but prepared sections frequently reveal that the specimen consists only of surrounding fat and fibrous capsule.

Large, slowly growing tumors are often surrounded by a rather resistant layer of connective tissue and fat. This layer of adipose tissue together with the deeper fibrous tissues should be carefully incised and retracted in order to expose the true capsule of the tumor. Lymphomas are generally friable and soft; therefore it may facilitate matters to sacrifice a portion of the true capsule in the wedge. The actual incision into the tumor should be as far removed from the cutaneous incision as is feasible and consistent with the exposure. A sharp scalpel should be used to excise the wedge; the specimen should be removed without trauma. The cautery, the electric knife or rough handling tends to destroy and distort the histologic character of the biopsy specimen. Postoperative fungation of the wound is minimized by shifting the fibrous capsule and obliterating the defect with adipose tissue. The skin should be approximated with fine silk or dermal sutures and the wound closed without drainage.

COMMENT

Two groups of patients are compared (tables 1 and 2) in which different technics for excising lymph nodes for biopsy were employed; group 1, in which silk and a more or less cramped technic were used, and

group 2, in which catgut and a less confining technic were employed. The results in group 1 showed excellent wound healing with cosmetically good scars and an average interval between biopsy and the onset of

TABLE 1 *(Group 1).—Small Incisions and Silk Technic*

Patient	Sex	Surgical Excision of Tissue	Institution of Radiation Therapy	Interval Between Biopsy and Institution of Therapy, Days	Histologic Diagnosis
B. H.	M	1/13/37	1/18/37	5	Hodgkin's disease
A. J.	F	1/28/37	1/28/37	0*	Reticulum cell lymphosarcoma
M. C.	M	2/18/37	2/25/37	7	Hodgkin's disease
J. G.	M	3/ 8/37	3/12/37	4	Reticulum cell lymphosarcoma
N. R.	M	3/ 9/37	3/12/37	3†	Giant follicle cell lymphosarcoma
J. S.	M	4/ 2/37	4/ 6/37	4	Hodgkin's disease
B. K.	M	4/30/37	5/ 5/37	5	Hodgkin's disease
A. G.	F	5/18/37	5/24/37	6	Reticulum cell lymphosarcoma
S. S.	M	6/ 9/37	6/14/37	5	Hodgkin's disease
A. M.	M	6/15/37	6/23/37	7	Lymphosarcoma
E. M.	F	6/25/37	6/29/37	4	Hodgkin's disease
J. E.	F	7/12/37	7/19/37	7*	Reticulum cell lymphosarcoma
				(Average, 4.7)	

* Wedge biopsy (previous doubtful aspiration biopsy).
† Suggestive aspiratons.

TABLE 2 *(Group 2).—Large Incisions and Catgut Technic*

Patient	Sex	Surgical Excision of Tissue	Institution of Radiation Therapy	Interval Between Biopsy and Institution of Therapy, Days	Histologic Diagnosis
R. W.	M	1/29/36	2/ 4/36	6	Lymphosarcoma
F. V.	M	2/10/36	2/16/36	6	Hodgkin's disease
W. S.	M	2/18/36	2/24/36	6	Lymphatic leukemia
V. G.	M	3/27/36	4/ 1/36	5	Hodgkin's disease
M. B.	F	4/20/36	4/27/36	7	Hodgkin's disease
F. P.	F	6/ 8/36	6/19/36	11*	Hodgkin's disease
A. H.	M	8/ 5/36	8/ 5/36	0†	Lymphosarcoma
E. C.	M	8/28/36	9/ 3/36	6	Hodgkin's disease
C. L.	M	10/28/36	11/ 3/36	6	Hodgkin's disease
A. S.	F	11/27/36	12/ 8/36	11*	Hodgkin's disease
L. G.	M	2/ 5/37	2/19/37	14*	Hodgkin's disease
Sy. S.	M	2/11/37	2/20/37	9	Hodgkin's disease
D. F.	M	3/29/37	4/ 6/37	8	Giant reticulum cell lymphosarcoma
R. L.	M	5/ 7/37	5/13/37	10*	Hodgkin's disease
L. J.	F	5/19/37	5/25/37	7	Hodgkin's disease
N. L.	M	6/15/37	6/23/37	8	Hodgkin's disease
J. W.	M	6/18/37	7/ 1/37	13*	Reticulum cell lymphosarcoma
				(Average, 6.1)	

* Cases omitted in computing average interval.
† Suggestive aspirations.

treatment of four and seven-tenths days. The results in group 2 were less gratifying, with delayed healing, drainage of lymph and an average interval before treatment of six and one-tenth days.

The 12 patients in group 1 were managed by the same surgeon, and in the beginning the technic was used for cosmetic reasons primarily

and without any definite idea of speeding up the application of roentgen therapy. It was then observed that the patients had very little reaction around the wounds. The incisions were healed and ready for roentgen therapy approximately on the day that the histologic report became available (four day interval). The minimum wound reaction and the rapid healing in the patients of group 1 seemed to indicate that immediate roentgen therapy probably would not have altered wound healing. No more than three skin sutures were used, and in most instances only two were used. In 4 of the 12 patients the skin was approximated with a single suture. In general, the conclusions from this comparison are summarized in table 3.

Eleven different surgeons performed the 17 biopsies in group 2. Eight surgeons performed 1 biopsy each; one surgeon performed 2, one 3 and another 4. Therefore, for strictly comparative results between catgut and silk technic or for any other particular feature of surgical

TABLE 3.—*Comparison of Results with Different Technics*

	Silk Technic, Small Incisions		Catgut Technic, Large Incisions	
	Advantages	Disadvantages	Advantages	Disadvantages
Patient.....	Negligible scar Minimum complications Minimum delay	None	None	Ugly scar Wound may fungate
Surgeon.....	Favorable results	Time consuming	Technically easy	Longer postoperative care; more complications

technic these results are of little value and are presented only for their general interest as related to the problem of biopsy in the lymphomatous diseases. As may be noted in table 2, 5 of the cases are omitted in computing averages because of the unusually long delay before treatment was started. Ordinarily the interval between biopsy and the institution of therapy is approximately four days (interval for routine section). The decision to begin or to delay therapy may be due to the condition of the wound or to the patient's inability to fill an early appointment, due to employment, distance from the hospital, sickness in the family, bad weather or holidays. Also, the general physical condition may be such that a delay in treatment is deemed advisable in order to allow the patient to recover from a temporary secondary infection.

Such factors as those mentioned should apply about equally to both group 1 and group 2 despite the small sampling of patients. In group 2 5 of the 17 patients had a delay of ten days or more owing to a combination of poor healing, weakness, lymph drainage and the other general causes of delay mentioned. Discounting these 5 patients, the residual 12 in group 2, when compared with the 12 of group 1, showed an average delay of an additional day and a third.

In 1 instance in each of the two groups treatment was started the day surgical excision of biopsy material was performed, owing to suggestive histologic evidence obtained from previous needle aspirations. The aspirations had been performed during an earlier stage of the disease, in which lymph nodes were inaccessible for excision. Subsequently, in 1 instance a "wedge biopsy" was performed; in the other a deeply situated node was dissected free and excised.

SUMMARY AND CONCLUSIONS

At the Memorial Hospital, surgical excision of an involved lymph node is the method of choice for obtaining biopsy material in the lymphomatous diseases. For certain patients it is necessary to repeat the procedure during the course of the disease in order to establish a definite diagnosis.

In this group of diseases, needle puncture and aspiration are reserved for patients in whom there are no accessible diseased lymph nodes suitable for excision and for whom removal of a wedge is not feasible. Smears of aspirated material are supplemented when possible by additional biopsy material obtained during the course of the disease.

The selection of a suitable diseased lymph node for surgical removal deserves the careful attention of the clinician.

Adequate small cutaneous incisions and careful aseptic silk technic minimize the undesirable postoperative complications of lymph drainage and wound separation.

MUSCULAR AND SKELETAL CHANGES IN ARACHNODACTYLY

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The syndrome now designated as arachnodactyly was first described by Marfan [1] in 1896. His patient, a girl 5½ years of age, had increased length and slenderness of the hands and feet, decrease in soft tissue, finger contractures, ligamentous relaxation and other associated congenital abnormalities. Because of the long, thin spider-like feet he called the condition "pieds d'araignée." The term arachnodactyly ("spider digits") was first used by Achard [2] in 1902.

Young [3] reviewed 22 cases of arachnodactyly reported between 1896 and 1929 and added 4 cases. Weve [4] in 1932 described 23 cases in six families, bringing the total number of cases reported at that time to 84. He emphasized the familial and hereditary characteristics of the condition. Since Weve's report 48 cases have been added to the literature. Reports of only 37 cases have appeared in the American literature since Piper and Irvine-Jones [5] described their case in 1926. Pediatricians gave most attention to this condition until Ormond,[6] in 1924, emphasized the important ophthalmologic features. Since that time the majority of reports have appeared in the ophthalmologic journals and have dealt chiefly with the ocular findings. The abnormalities associated with arachnodactyly are not ordinarily detected until the second or third year of life. There is either actual or apparent lengthening of the hands and

From the Department of Surgery, Division of Orthopedic Surgery, University of Chicago Clinics.

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2. Achard, C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834, 1902.

3. Young, M. L.: Arachnodactyly, Arch. Dis. Childhood **4**:190, 1929.

4. Weve, H.: Ueber Arachnodaktylie (Dystrophia mesodermalis congenita, Typus Marfan), Arch. f. Augenh. **104**:1, 1931.

5. Piper, R. K., and Irvine-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Disease: Report of a Case and Review of the Literature, Am. J. Dis. Child. **31**:832 (June) 1926.

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feet, particularly the fingers and toes. The face may have an appearance of maturity because of a decrease of subcutaneous tissue. Roentgenograms of the hands and feet usually show long, thin bones with a decrease in soft tissue. The patients grow rapidly in height. Skeletal development is in advance of chronologic age in many cases. The soft tissue about the extremities is poorly developed. There are ligamentous relaxation and, occasionally, contractures of the fingers. Spinal curvature in early childhood is common. Dislocation of the lenses associated with other ocular anomalies has been found in over half the reported cases. The external ear may be large, with poorly developed cartilaginous structure. The palate in many cases is curved and highly arched. The intelligence in most instances is normal. The condition may be sporadic or familial. The incidence in the two sexes is equal.

REPORT OF CASES

CASE 1.—G. D. (fig. 1), a boy aged 5½ years, was brought for examination because of weakness, thinness of the extremities, curvature of the spine and near-sightedness. He was delivered at full term by instruments but without difficulty. The weight at birth was 7 pounds and 10 ounces (3,405 Gm.). The child started to walk at 13 months of age, and the gait was always unsteady. The parents believed that he was not as strong as other boys of the same age and observed that he was near-sighted. Curvature of the spine was first noticed during the fourth year and had gradually progressed. The patient was an only child. The parents, who were of Greek origin, showed none of the characteristic abnormalities of arachnodactyly, and no evidence of the disorder could be found in other members of the family.

Examination.—The patient was very tall for his age; the standing height was 55.4 inches (140 cm.) and the weight 59 pounds (26.8 Kg.). The gait was unsteady. The skull was symmetric except for slight prominence of the forehead. The ears were large. The teeth were normal. The palpebral fissure of each eye was oblique, this peculiarity being more marked on the right side. The external conjugate movements of the eyes were full and synchronous. The tactile tension was normal. There was no abnormality of the cornea of either eye. The iris was tremulous in both eyes. The lenses were clear and were dislocated downward and temporally. The zonular fibers were seen in the aphakic portion of the pupil. The fundi were normal. The vision was not improved by lenses. The palate was highly arched and narrow. Mild "right dorsal and left lumbar" scoliosis (fig. 3*A*) was present. The pelvis appeared broad. The subcutaneous tissue of the extremities was decreased, exaggerating the length of the hands and feet (fig. 2). Measurements did not reveal, however, that the bones of the hands and feet were relatively increased in length as compared to the long bones. The fingers could be extended 20 degrees beyond the normal limits at the metacarpophalangeal joints. A similar but less marked relaxation was noted in other joints. A roentgenogram of the spine (fig. 3*A*) showed thoracolumbar scoliosis. Roentgenograms showed the bones of the right forearm and hand (fig. 3*B*) and the right foot (fig. 4*B*) to be advanced in development. The bones of the extremities

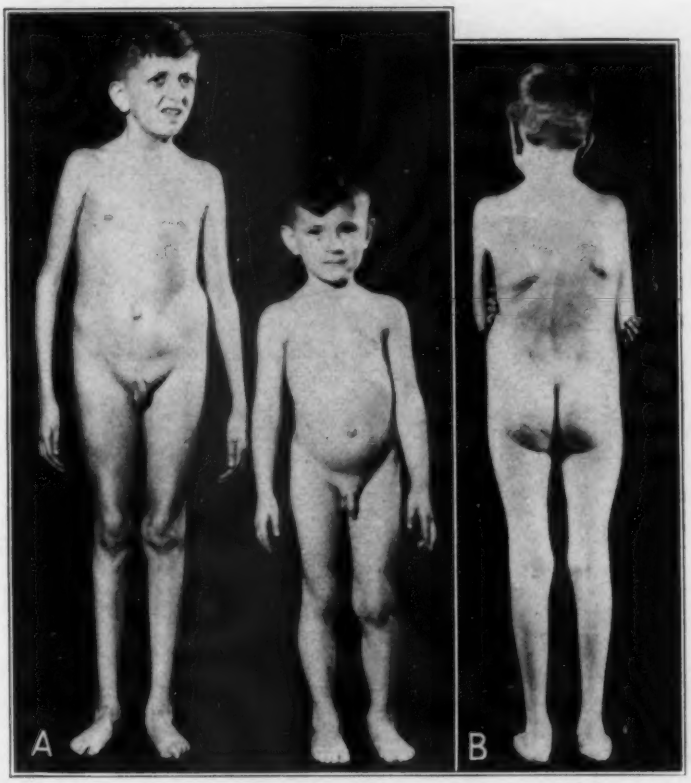

Fig. 1 (case 1).—*A*, comparison of G. D., a boy aged 5½ years (left), with a normal child of the same age. Note the long, thin extremities, the large ears and the oblique position of the eyes. *B*, posterior view, showing dorsal scoliosis toward the right, with winging of the scapulas. The loose adipose tissue about the hips is well visualized. Bilateral dislocation of both lenses and iridodonesis are present.

Fig. 2 (case 1).—*A*, hands of the patient. The fingers are long, with thin soft parts. *B*, photograph of the feet, showing pronation and long, thin toes. General ligamentous relaxation is present.

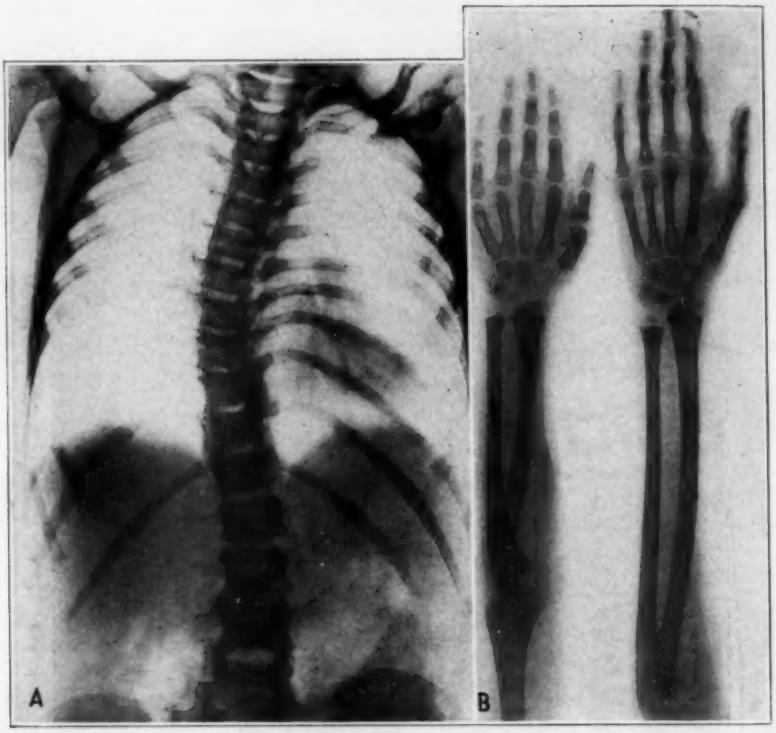

Fig. 3 (case 1).—*A*, roentgenogram of the spine, showing thoracic scoliosis toward the right. *B*, roentgenogram of the right forearm and hand of the patient (right) in comparison with those of the same normal child (left) as in figure 1 *A*. The bones of the upper extremities are developed out of proportion to the age. All centers of ossification in the carpus bone are present, while in the normal child only three are well ossified.

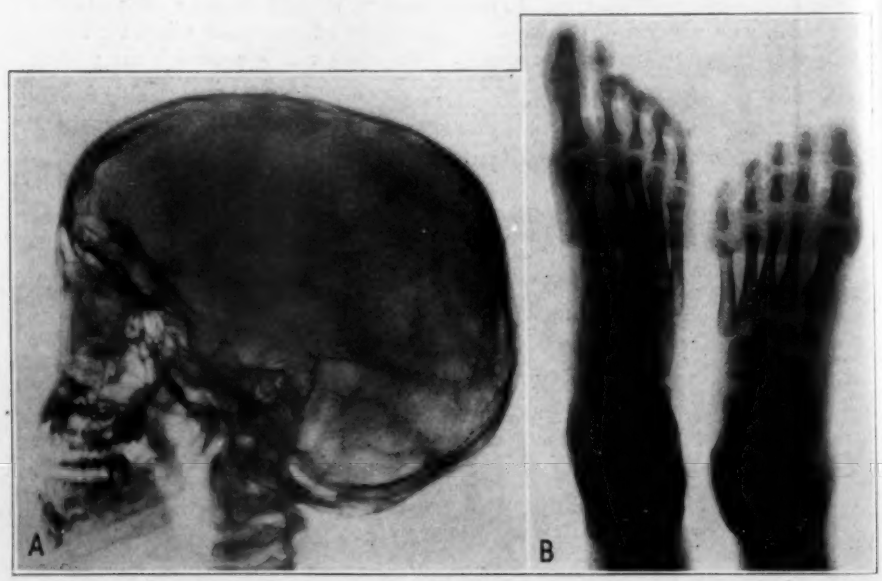

Fig. 4 (case 1).—*A*, lateral roentgenogram of the skull, showing a deep sella turcica and a small anterior fossa. *B*, roentgen comparison of the feet of the patient (left) and those of the normal child. The feet of the patient are long and the bones relatively thinned.

were narrowed out of proportion to their length. A roentgenogram of the skull (fig. 4 *A*) showed a slightly deepened sella. The sinuses were large, and the anterior cranial fossa was decreased. Routine examination of the blood and urine showed them to be normal. The value for blood calcium was 11.03 mg. and that for phosphorus 3.88 mg. per hundred cubic centimeters. Microscopic study of tissue removed from the gastrocnemius muscle showed it to be of normal structure. The intelligence quotient was 96 (Stanford Binet).

Case 2.—M. P. (fig. 5 *A*), a girl aged 25 months, was seen because of poor general health, deformities of the hands and feet and poor vision. She was an only child, born of parents in the fourth decade. At infancy it was noticed that the hands and feet were long and slender. She walked at 18 months. Five months

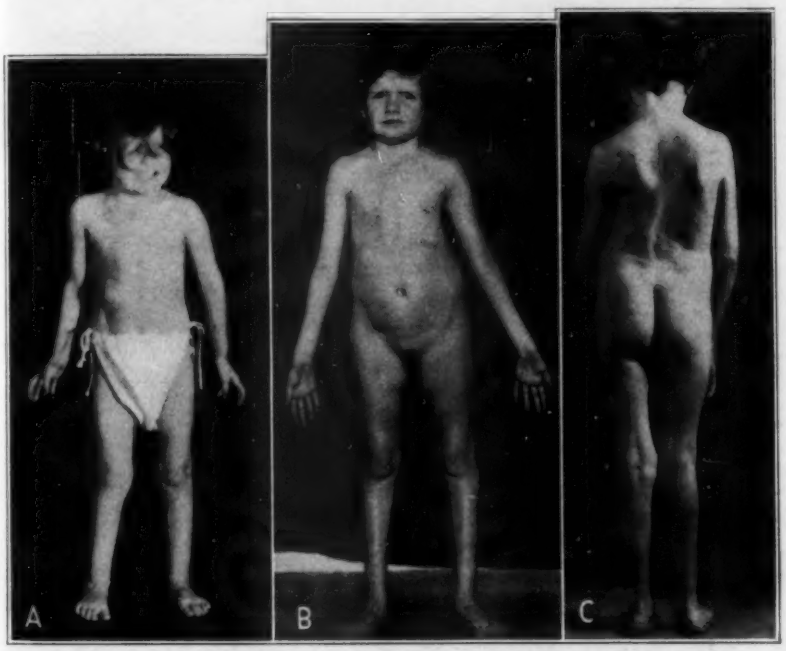

Fig. 5 (case 2).—*A*, M. P., a girl aged 25 months. Note the long slender hands and feet and the thinness of soft tissue of the extremities, particularly the fingers and toes. Subluxation of both lenses, iridodonesis and hydrophthalmos are present. *B*, same patient at the age of 5 years and 2 months. The feet are pronated, and there is general relaxation of the ligaments. *C*, posterior view, showing thoracic scoliosis on the right and lumbar scoliosis on the left.

prior to observation a spinal curvature was first observed. Visual disturbance had been present for several months. The mental development was normal. There was no family history of similar difficulty.

Examination.—The head was slightly larger than normal but was symmetric. The ocular movements were normal. The palpebral fissures were equal. Each cornea measured about 14 mm. in horizontal and in vertical diameter. The

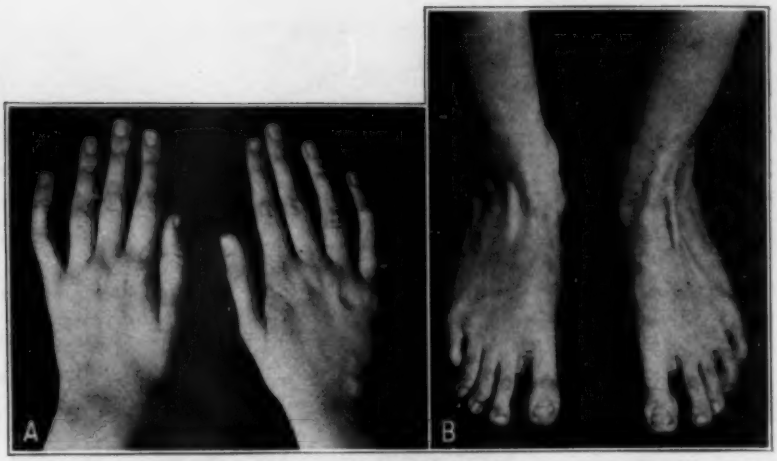

Fig. 6 (case 2).—*A*, hands of M. P., showing the long slender fingers and toes. *B*, feet of the same patient. The feet are pronated, long and slender. The phalanges are exaggerated in length by the thinness of the soft tissue.

Fig. 7 (case 2).—*A*, roentgenogram of the right hand, showing the long narrowed metacarpals and phalanges, with a decreased soft tissue shadow. Note the abnormally advanced ossification of the carpus bone (patient's age, 5 years). There is mild thinning of the bones of the foot (*B*). The phalanges of the fifth digit are deformed.

anterior ocular chambers were extremely shallow. The irises were tremulous and somewhat atrophic as demonstrated by transillumination. The right pupil measured 1 mm. and the left 2.5 mm. in diameter. The tactile tension was normal in both eyes. The right pupil dilated to 3 mm. on administration of atropine, but no increase in size was noted in the left. Both lenses were dislocated upward and outward. The right disk had a temporal conus, but no temporal pallor of either disk was seen, and there was nothing to suggest glaucomatous excavation. A diagnosis of hydrophthalmos and subluxation of each lens was made. The palate was high and narrow. Dentition had proceeded normally. Mild scoliosis to the

Fig. 8 (case 3).—*A*, M. S., a girl aged 15 years, with upward and inward dislocation of both lenses, myopia and bilateral iridodonesis. Note the pigeon breast deformity and the long slender hands and feet. *B*, mild curve in the lower thoracic portion of the spine, with prominence of the right scapula. Hyperextension of some of the terminal phalanges is present, due to ligamentous relaxation.

right in the dorsal region was present. The feet and hands appeared long and slender, particularly the fingers and toes. There was a blunt projection of soft tissue between the first and second toes of both feet and one lateral to the base of the third left toe. Because of ligamentous relaxation, the range of motion was abnormally great in the joints of the hands and feet. A decrease of subcutaneous tissue exaggerated the length of the fingers and toes. Neurologic examination gave negative results.

The patient was again seen when she was 5 years of age, because of increasing scoliosis. A roentgenogram (fig. 7) of the right foot at that time showed no evidence of bony deformity at the site of the soft tissue prominences. The metacarpal bones, metatarsal bones and phalanges were long and narrow, and the soft tissue about them was decreased. The narrowing was especially noticeable near the center of the diaphysis. Bowing of the fifth finger and phalangeal deformities

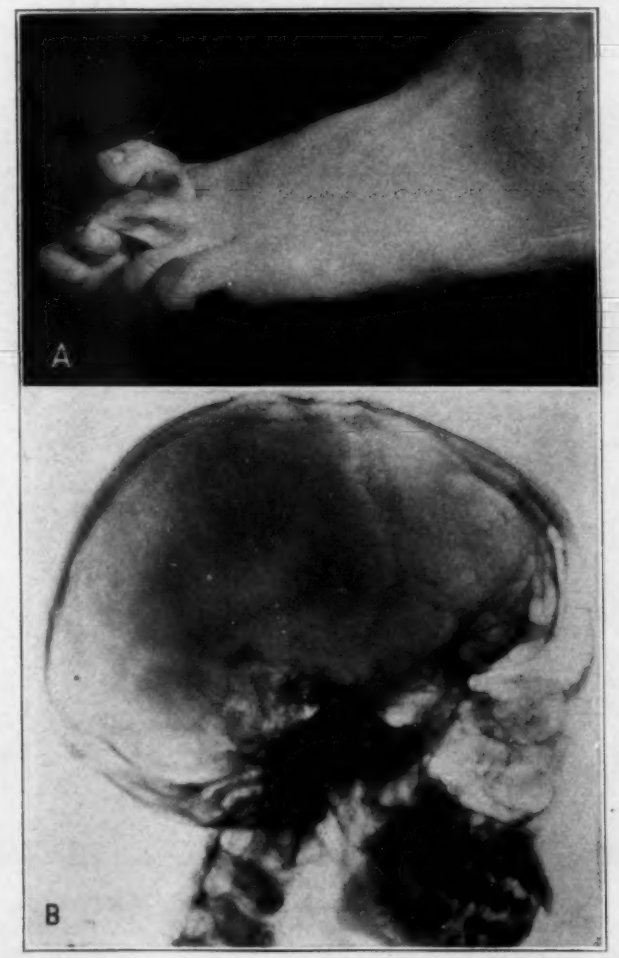

Fig. 9 (case 3).—*A*, foot of M. S. The second and third digits are extended to show the web contracture of the skin on the ventral surface. *B*, lateral roentgenogram of the skull, showing a normal sella.

of the fifth toe were present. All the centers of ossification were well defined and were in advance of the child's age. Roentgenograms showed no abnormality of the skull.

Case 3.—M. S. (fig. 8), a girl aged 15 years, came to the clinics because of frequent attacks of headache. She had worn glasses since the age of 6 years.

She stated that the optimum distance for reading was 4 inches (10 cm.). As far back as she could remember, friends had remarked about her long feet and hands. Her father, mother, two brothers and two sisters had ocular defects but no skeletal manifestation of arachnodactyly.

Examination.—The skull was of normal shape. The left eye was slightly higher than the right. The anterior chambers were deeper than normal. The lenses were dark red with a black rim. They were dislocated upward and inward and occupied four fifths of a 6 mm. oval pupil. The remaining one fifth of each pupil formed a crescent of clear red through which the fundi could be seen. Dentition

Fig. 10 (case 4).—*A,* M. T., a man aged 46 years. Blindness in the right eye resulted from uveitis peracta. Note the long, slender extremities with muscle thinness, which is exaggerated on the distal portion of the extremities. Note the wide pelvis. *B,* feet of the same patient (left) contrasted to a normal adult's foot.

was normal. The palate was high, narrow and arched, curving anteriorly to the right. A pigeon breast deformity was present (fig. 8 *A*). The heart and lungs were normal. There was a mild dorsal curvature with the usual prominent right scapular flare (fig. 8 *B*). The extremities appeared longer and were thinner than normal. The hands were long and slender but not relatively increased in length as compared to the other long bones. The thinness of the soft tissue was most marked about the fingers. Contracture of the soft tissue on the palmar surface of

the metacarpophalangeal joint of the third, fourth and fifth fingers was noted. The wrists and the terminal phalanges were hyperextensible. The four lateral toes of each foot were contracted by a cutaneous web (fig. 9 *A*). A lateral roentgenogram of the skull (fig. 9 *B*) showed the sella and the general architecture of the skull to be normal.

Fig. 11 (case 4).—Comparison of the patient's hands with the hand of a normal person. *A*, palmar aspect; *B*, dorsal aspect. Note the contractures of the fingers.

Case 4.—M. T. (fig. 10 *A*), a man aged 45, was seen because of pain in the suboccipital region, loss of memory and spots before the eyes. Four years prior to admission he noticed floating spots before his eyes. Examination at that time revealed hemorrhages into the right retina. Shortly after this, vision became defective on that side. He had had intermittent pain which radiated from the right frontal to the occipital region. Contractures of the fingers and toes had been present since birth. Constant stretching improved the deformities of the fingers.

In childhood it was possible to dislocate the patellas at will. No dislocation had occurred in the last few years, and it appeared that the patellas had become more stable. The feet were long, a size 12 shoe being required. His father, his paternal grandfather, a sister and her two daughters, who were half-sisters, had similar deformities (fig. 12). One sister was living and had no abnormalities.

Examination.—The patient weighed 184 pounds (83.5 Kg.). The head was of normal shape. The cornea of the right eye was clear. The media were cloudy, and the iris appeared dull. The anterior chamber was shallow, owing to

Fig. 12 (case 4).—Family of the patient. *A*, paternal grandfather; *B*, father; *C*, brother; *D*, sister. All have long, thin, contracted fingers and slipping patellas. *E*, daughters of *D*, one aged 16 years, with contracted fingers and slipping patella, the other aged 6 years, with no deformities. *F*, half-sister of patients in *E* and daughter of *D*. Note the long fingers with contractures. *G*, elder sister (*E*) in infancy. *H*, the earliest photograph of the patient.

bulging forward of the iris. The lens was moderately opaque. The disk was not seen. The pupil was contracted and fixed. The tension of the right eye was 13 and that of the left 19 (Schiötz-Gradle). A diagnosis of uveitis peracta of the right eye was made, and enucleation was performed. The ears were normal. The palatal arch was not high. The teeth were normal. Except for a mild dorsum rotundum no deformity of the spine was noted. The hips were wide and the adipose

tissue increased. The extremities distal to the elbows and knees appeared long and thin. The fingers were contracted at the metacarpophalangeal and interphalangeal joints. The thumbs were not affected, and the index finger was affected to a slighter degree than the remaining ones. The contractures were most marked at the proximal interphalangeal joints, the third and fourth fingers having the most marked deformity. These two fingers were contracted nearly 45 degrees at

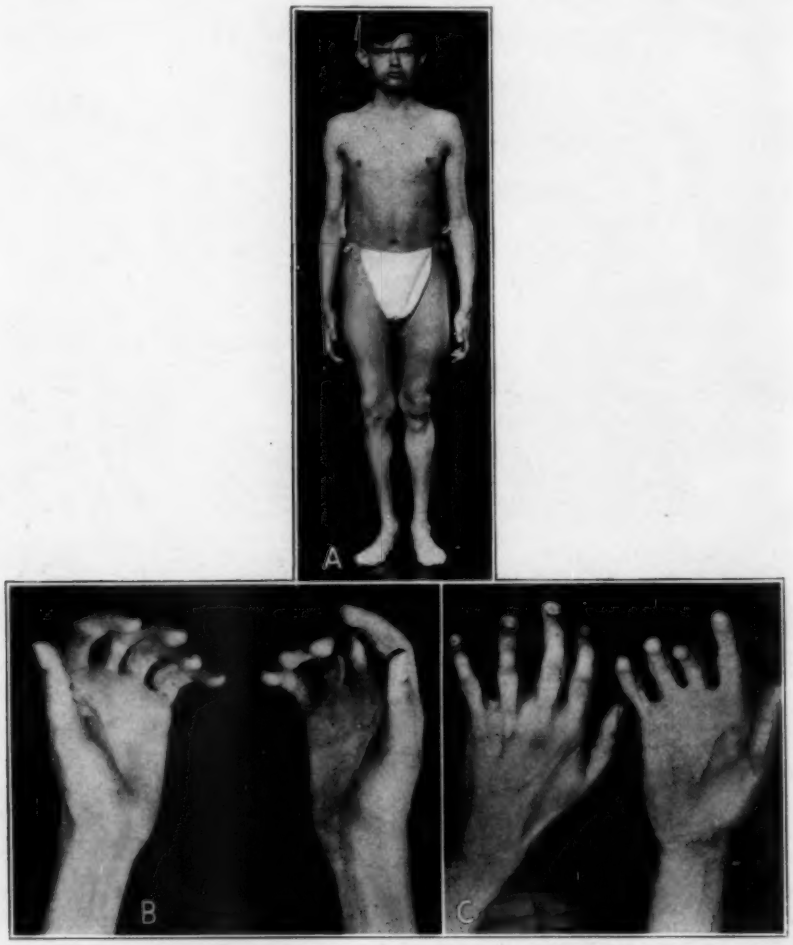

Fig. 13 (case 5).—*A*, photograph of R. G. at the age of 16 years. The right patella is abnormally high, and there is wasting of the vastus medialis muscles, more pronounced on the right. *B*, appearance of the hands at the age of 14 years, with the fingers in maximum extension. *C*, improvement in contracture of the fingers following treatment. The contracture is most marked in the middle fingers.

this joint. The metacarpophalangeal and the distal interphalangeal joints showed only slight contracture. Flexion of the terminal phalanges was limited to half normal. The little finger of each hand was curved toward the ring finger (fig. 11). The soft tissue of the extremities was considerably reduced. The lower portion

of the vastus medialis muscle on both sides was poorly developed. The patellar ligaments were long and relaxed. The patella was abnormally high on each femoral condyle and displaced laterally. The digits were not relatively increased in length. The toes were long and slender and were contracted to a slighter degree than the fingers. The first toe, like the thumb, was not contracted. Roentgenograms of the skull showed some abnormal calcification of undetermined nature adjacent to the pineal body. The sella and the general shape of the skull were normal. Microscopic examination of a piece of gastrocnemius muscle showed normal striated muscle. No increase in glycogen could be demonstrated by Best's carmine technic.[6a]

CASE 5.— R. G. (fig. 13 *A*), a boy aged 14 years, was seen because of repeated displacement of the left patella. He was born at full term by instrumental delivery and weighed 9½ pounds (4,309 Gm.). He started to walk and to talk at the normal age. Dislocation of the patella first occurred at the age of 8 years and was spontaneously reduced. Contractures of the fingers and toes were noted by his parents at his birth. His intelligence was normal. The father had no deformi-

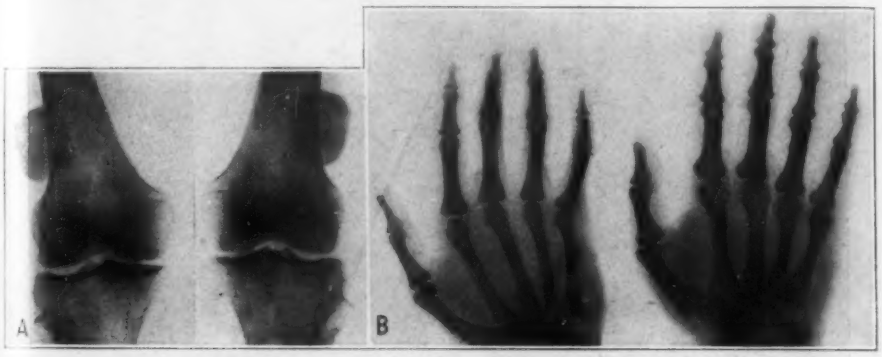

Fig. 14 (case 5).—*A*, roentgenogram of the knees, showing bilateral dislocation of the patella and a prematurely closed epiphysis. *B*, roentgenogram of the hand (left) contrasted with the hand of a normal adult. Note the abnormally wide articular cartilage space of the metacarpophalangeal joints of the thumb and index fingers. The heads of the metacarpal bones are widely separated. The ring finger is the longest digit of the patient's hand.

ties. One sister, 12 years of age, was normal. His mother (fig. 15 *A*) and maternal grandmother had similar deformities.

Examination.—The patient weighed 118 pounds (53.5 Kg.) at the age of 16 years and was 66.1 inches (195.5 cm.) tall. His head was of normal shape. The ears were large, and the cartilaginous structures were poorly developed. The antitragus of each ear was enlarged. The eyes were normal. The chest was long, with a narrow sternum and a mild pigeon breast deformity. There was a soft systolic murmur at the base of the heart. No curvatures or deformities of the spine were noted. The extremities were long and the subcutaneous tissue scanty. The fingers were contracted at the metacarpophalangeal and interphalangeal joints

6a. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technique: Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological, ed. 2, New York, D. Appleton-Century Company, 1938.

(fig. 13 *B*). All the fingers were involved except the thumbs, the index fingers to a less degree than the medial three fingers. The interphalangeal joints of the ring and middle fingers showed the greatest degree of contracture. There were no contractures at the shoulders, elbows or wrists. The soft tissues of the extremities were scanty. Each vastus medialis muscle was underdeveloped in its lower portion. Both patellas were abnormally high and displaced outward on the lateral femoral condyles. The patellar tendons were long and relaxed, permitting the patellas to move abnormally high when the quadriceps femoris muscle contracted. The last 10 degrees of extension was done with difficulty because of the relaxed

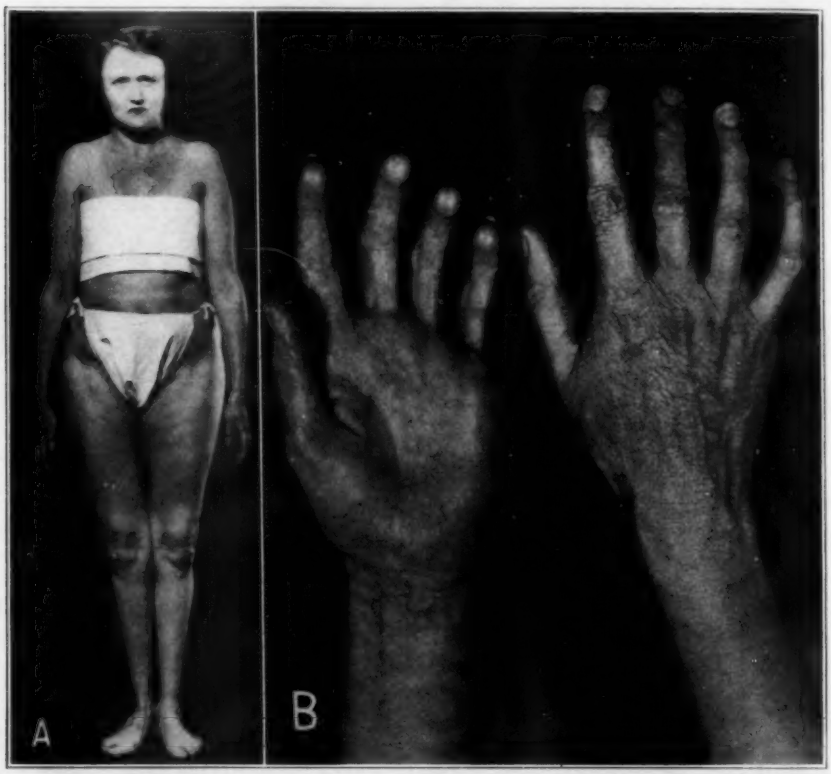

Fig. 15 (case 6).—*A*, M. G., a woman aged 36 years (mother of R. G. [case 5]). Note the long contracted fingers, the straight forehead and the soft tissue thinness of the extremities. *B*, photograph of the hands, showing contracture of the fingers, most marked in the fifth digit. The soft tissue of the fingers is small.

patellar tendons. There was mild contracture of the four lateral toes by shortness of the soft tissue. A Goldthwait operation was performed to correct the slipping patella on the left. At operation the patellar tendon was found to be about three times the normal length. The contracted fingers were improved by use of intermittent traction and passive stretching. A photograph (fig. 13 *C*) taken at the age of 16 years, two years after the time when he was first seen, showed an improvement in the flexion contracture deformity of the fingers. A roentgenogram of the hand (fig. 14 *B*) showed long, narrow metacarpal and phalangeal bones.

The fingers were slightly curved toward a line between the middle and ring fingers. The spaces between the heads of the metacarpal bones appeared to be abnormally wide. The articular cartilage space of the metacarpophalangeal joints of the thumb and index fingers was unusually wide. The fourth finger was the longest, whereas in the normal hand the third digit is the longest.

CASE 6.—M. G. (fig. 15 *A*), aged 36 years, mother of R. G. (case 5), had had recurrent dislocation of both patellas since the age of 11 years. Dislocations had at first occurred as many as four times a year, but had ceased during recent years. Contractures of the fingers and toes had been present as long as the patient could remember. There had been a gradual improvement in the finger deformities with constant stretching. The patient's mother had similar contractures of the fingers and toes. There has been no difficulty with vision.

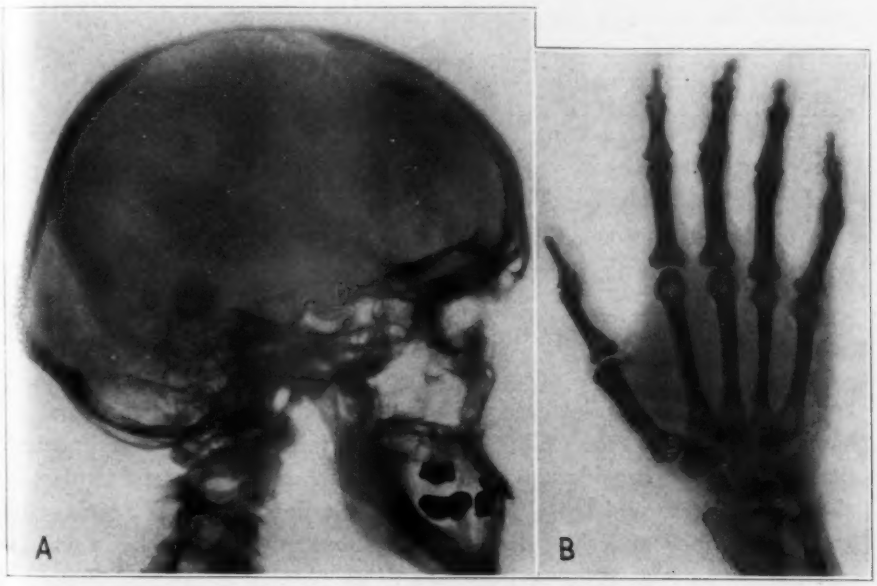

Fig. 16 (case 6).—*A*, lateral roentgenogram of the skull of M. G., showing a moderate degree of prognathism. The sella is normal. *B*, roentgenogram of the right hand, showing slender bones and scanty soft parts. The articular cartilage space of the metacarpophalangeal joints of the thumb and index fingers is unusually wide. The fifth digit is curved inward.

Examination.—The patient was 63.7 inches (162 cm.) tall and weighed 128 pounds (58.1 Kg.). The forehead was straight. There was a moderate degree of protrusion of the mandible. The cartilaginous structures of the ears were poorly developed. The eyes were normal. There was no spinal deformity. A pigeon breast deformity was present. The extremities were long and slender. The soft tissue about the hands was considerably reduced, exaggerating the length of the fingers. The patellas were displaced upward on the lateral femoral condyles, and the patellar ligaments were elongated. The fingers, with the exception of the

thumb, were contracted at the metacarpophalangeal and interphalangeal joints (fig. 15 *B*). The first phalanges could be extended to within 10 degrees of normal. The interphalangeal joints of each digit were equally contracted. The medial fingers showed the most pronounced contracture. While there was some decrease from the normal in the circumference of the legs and forearms, this was more evident about the digits. A roentgenogram of the hand (fig. 16 *B*) showed slender bones and scantiness of the soft parts. The lateral curvature of the little finger and the medial curvature of the middle finger were exaggerated. The articular cartilage space of the metacarpophalangeal joints of the first and second fingers appeared unusually wide (fig. 16 *B*). The hands and feet were not elongated out of proportion to the height. There was no contracture of the toes. A lateral roentgenogram of the skull showed mild prognathism and a normal sella turcica (fig. 16 *A*).

ETIOLOGIC AND FAMILIAL ASPECTS

The cause of arachnodactyly is as obscure as that of other congenital abnormalities.

There is a family history connected with over half the reported cases. Weve [4] reported 23 cases in six families and called particular attention to the familial tendency. Typical cases occur in families without a history of the disease on either side (cases 1, 2 and 3). Either sex may transmit the condition through three or four generations.

CHANGES IN SOFT TISSUE

In all cases there is a decrease of soft tissue in some portion of the body. Because of this decrease and wrinkling of the skin the face usually has an aged appearance. While soft tissue is fairly well preserved about the pelvis, it is considerably reduced in the extremities, particularly about the fingers and toes. The term muscle dystrophy has been used to describe the smallness of the soft tissues, but this term implies a wasting disease, such as primary muscular dystrophy.

That arachnodactyly may be a form of primary muscular dystrophy has been suggested. Spinal deformity, decrease of soft tissue and a familial tendency are common in both conditions. The difference between these syndromes, however, is more striking than their similarities. The apparent muscular atrophy in arachnodactyly is present at birth and is not progressive, and weakness is proportional to the size of the underdeveloped muscles. Microscopic examination of muscle from 2 patients (cases 1 and 4) showed normal muscle tissue.

Thursfield [7] stated the opinion that the muscular involvement in arachnodactyly and that in amyotonia congenita are similar in some respects. In amyotonia congenita or Oppenheim's disease, however,

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7. Thursfield, H.: Arachnodactyly, St. Barth. Hosp. Rep. **53**:35, 1917.

there is marked muscular atony without apparent muscular atrophy. The condition tends gradually to improve. Microscopic examination of muscle shows muscle fibers of normal size intermingled with many small fibers. The fibers retain their normal striated appearance.

LIGAMENTOUS RELAXATION AND CONTRACTURES

Some type of ligamentous relaxation is always present and is usually most pronounced in the joints of the hands and feet. In cases described by Patterson [8] and by Burch [9] there was marked relaxation of the sternoclavicular joint, with subluxation. The patellar ligaments are frequently elongated, with the patellas located laterally and superiorly on the femoral condyles, making the last few degrees of extension difficult. There may be elongation and relaxation of the patellar ligaments without a history of dislocation. The patellar ligaments in 1 patient (case 5) were nearly three times as long as normal, and he had had repeated displacements. A roentgenogram revealed no abnormality of the femoral condyles. Two adult patients (cases 4 and 6) who had had recurrent dislocations in childhood had not observed recurrence for some years prior to observation. It seemed that stability in this region was increasing with advancement of age. Each of the 3 patients (cases 4, 5 and 6) who gave a history of dislocation of the patellas showed underdevelopment of the lower and medial portions of the vastus medialis muscle. When contractures occur, the fingers and toes are usually involved, but occasionally only the larger joints are affected. A similar pattern of contracture about the hands was noted in cases 3, 4, 5 and 6. In none of these cases was any involvement of the thumb apparent, and the index finger was less affected than the other digits. In 3 cases (cases 4, 5 and 6) the metacarpophalangeal and interphalangeal joints were contracted and the palmar soft tissues shortened. In these cases the maximum contracture was found at the interphalangeal joints. In another case (case 3) the patient had contractures only at the metacarpophalangeal joints. In this case there was relaxation of the interphalangeal joints, resulting in hyperextension when the hand was opened. The interphalangeal joints of the middle finger of each hand in 1 patient (case 5, fig. 13) showed the most marked contracture. His mother (case 6, fig. 15 *A*) showed approximately the same degree of contracture of the interphalangeal joints of each finger, the contracture increasing from the index to the little finger of each hand. In case 4 the most

8. Patterson, W. J.: Case of Arachnodactyly, Canad. M. A. J. **28**:652, 1933.

9. Burch, F. E.: Association of Ectopia Lentis with Arachnodactyly, Arch. Ophth. **15**:645 (April) 1936.

prominent contracture occurred at the proximal interphalangeal joints of the third, fourth and fifth fingers. The little finger in cases 2, 4 and 6 was curved laterally. In 3 of the cases in which contracture of the finger was present there was some degree of contracture of the toes (cases 3, 4 and 5), the middle digit in each instance exhibiting the greatest deformity.

SKELETAL ANOMALIES

Persons with arachnodactyly are usually taller than normal persons and weigh less. The hands and feet are apparently or relatively lengthened. There was an apparent increased length of the fingers in all the cases reported here, with the exception of 1 case (case 5), because of decreased soft tissue. Measurements, however, indicated that there was no relative increase in length of the bones of the hands and feet as compared with other long bones. In 3 patients (cases 1, 2 and 4) an apparent increase in length of the toes was found.

Spinal deformity is commonly associated with arachnodactyly. In the 52 cases in which deformity was mentioned, scoliosis was present in 37, kyphoscoliosis in 8 and kyphosis in 7. The deformity usually appears in early life and is slowly progressive, but in most instances it does not become severe. It has been attributed to a poorly developed muscular system. Increased length of the spinal column may also be a factor. Moderate thoracic scoliosis was present in cases 1, 2 and 3. The onset in 1 patient (case 2) was noticed at 18 months; in another it was first observed at 4½ years (case 1). The curvature in 1 patient had its onset much later.

Deformities of the head are present in approximately 75 per cent of cases. Dolichocephalus, prognathism, narrow arched palate and asymmetry of the skull are among the common anomalies. Dolichocephalus was mentioned in 17 cases but could not be demonstrated by measurements in the cases reported here. In some instances the head is relatively increased in size, while in others it is smaller than normal, as was noted by Weill.[10] Roentgenograms of the skull in some cases have revealed prominence of the orbital roof with a corresponding shortening of the anterior cranial fossa. In 1 of the cases reported here this abnormality was noted (case 1). In 9 of the reported cases the sella was believed to be slightly reduced in size. In 9 cases there was protrusion of the chin. An example of this is illustrated in case 6. In cases 1, 2 and 3 the palate was high and narrow, and in 1 of these (case 3) it was curved to the right.

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10. Weill, G.: Ectopie des cristallins et malformations générales, Ann. d'ocul. **169**:21, 1932.

Deformities of the chest wall have been noted in nearly 50 per cent of the cases. A narrow flat chest, a funnel-shaped breast, projection of the lower part of the sternum and pigeon breast are some of the more common anomalies. A pronounced pigeon breast deformity was present in cases 3 and 6. The ears are frequently malformed. Enlargement of the lobes was the most frequent defect observed. In cases 1, 5 and 6 the lobes were large and flabby because of poorly developed cartilage. In some instances the crus helicis, antihelix and tragus are malformed.

HEART

Heart disease is a frequent accompaniment of the condition, about 35 per cent of patients showing some type of cardiac involvement. Piper and Irvine-Jones [5] found mention of a cardiac disturbance in 8 of the 18 reported cases. In 5 of these it was believed to be on a congenital basis. A patent foramen ovale was found at autopsy in Börger's [11] case. A deficiency of the interauricular septum was found in Piper and Irvine-Jones's [5] case. The usual finding is a systolic murmur over the apex. Burch [9] found cardiac symptoms in 4 of his 8 cases. One of the patients succumbed to heart disease. Only 1 patient (case 5) of this series was affected, and he had only a slight mitral murmur at the apex.

OCULAR CHANGES

The ophthalmologic features are those associated with ectopia lentis: iridodonesis, contracted pupils which react only sluggishly to atropine and irregularity of the anterior chamber of the eye. Bilateral dislocation of the lenses is the outstanding symptom. The lens may be dislocated in any direction, upper displacement being the common type. Although most authors speak of dislocation of the lens, it is actually subluxation in most cases. Complete dislocations have been reported by Thaden [12] and by Weve.[4] Young [3] in 1929 analyzed the 22 reported cases with 4 of his own. In 9 of these no mention was made of the ocular findings. Of the remaining cases, dislocation of the lenses was present in 30 per cent, iridodonesis in 38 per cent, miosis in 38 per cent, megalocornea in 8 per cent, a persistent pupillary membrane in 8 per cent, amblyopia in 8 per cent and a shallow anterior chamber in 8 per cent. The globes were deeply set in about 30 per cent. No abnormal changes were found in the fundi. Weve [4] found ocular complications in 50 per cent of 84 reported cases; in 33 per cent of these cases there was ectopia lentis. The lenses frequently show partial or complete opacity.

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11. Börger, F.: Ueber zwei Fälle von Arachnodaktylie, Ztschr. f. Kinderh. **12:** 161, 1914.

12. Thaden, F.: Ein Fall von Arachnodaktylie mit besonderer Berücksichtigung der Augensymptome, Arch. f. Augenh. **100**:278, 1929.

TREATMENT

Some patients with myopia and astigmatism have been benefited by suitable lenses. Improvement in vision usually results from removal of the lens in cases in which it is completely dislocated. Spinal curvature in none of these patients (cases 1, 2 and 3) was severe enough to require treatment. Pain in the foot may necessitate the use of supports. Finger contractures may be treated, with improvement in function (case 3).

SUMMARY AND CONCLUSIONS

1. Six cases illustrating various features of the syndrome of arachnodactyly are reported.

2. Microscopic examination of muscle tissue in 2 cases showed no pathologic change.

3. Certain roentgen and contracture peculiarities of the hands and feet have been pointed out.

REACTIONS OF THE PERITONEUM TO TRAUMA AND INFECTION

FURTHER EXPERIMENTAL STUDIES

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In a consideration of the more common complications which occur after abdominal operations it is evident that none is more serious than peritonitis and none more deserving of careful study from the standpoint of both prevention and cure. While the incidence of postoperative peritonitis has gradually and steadily declined during the past several decades, the possibility of its occurrence remains one of the chief hazards of operations on the lower part of the intestinal tract, and this is particularly true when resections or anastomoses which involve the large bowel are performed. The general decrease in the occurrence of postoperative peritonitis has been the result of (1) improvements and standardization in operative technic; (2) perfection in anesthesia, and (3) a greater realization of the importance of a proper period of meticulous preoperative care. During this period (seven to ten days or more) the fluid and electrolyte balances are restored and nutritional disorders are corrected. Thus, states of hypoproteinemia or anemia are corrected by blood transfusions, vitamin deficiencies overcome by the appropriate therapy and depleted glycogen stores replenished by a liberal carbohydrate intake.

For many years abdominal surgeons have observed and commented on the fact that the dangers of postoperative peritonitis are considerably less when laparotomies are performed on patients who have had colostomies or fecal or intestinal fistulas for some time than when the operation is performed on a patient with an intact, or virgin, peritoneum. Moreover, in the selection of the safest operative procedure in dealing with such lesions of the colon as carcinoma, it has been suggested by some writers that operation in stages is indicated, since, they contend, one of the chief advantages of the multiple stage procedure is the immunity conferred on the peritoneum by the first operation, which usually involves some form of intestinal anastomosis.

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About a year ago a series of experiments was conducted by Brinkman and one of us [1] in an effort to determine in a quantitative fashion the extent of such protection afforded by some of the more common abdominal operations. Dogs were used in the experiments, and a study was made of the effects of simple exploratory laparotomy as well as intestinal anastomoses performed at different levels in the digestive tract.

The conclusion from these earlier studies was that there is an enhanced resistance to infection which results from surgical manipulations in the peritoneal cavity. In dogs this is insufficient to protect the animal against a severe form of peritonitis, although such protection is possible by other means, e. g., intraperitoneal vaccination. A striking example of such protection is seen following the administration of a preparation of colon bacilli, aleuronat and tragacanth (coli-bactragen) developed by Steinberg. It was also concluded that phagocytosis in the peritoneal cavity is an important factor in the survival of dogs with acute peritonitis and that the polymorphonuclear leukocyte is the important cell in the phagocytosis and consequent recovery. It should be repeated here that in dealing with experimental peritonitis there are certain differences between the reactions of the peritoneum of the dog and that of man. In the dog, adhesion formation is minimal, there being little attempt at walling off of infections by the peritoneum. Furthermore, there are technical difficulties attendant on the production of a uniformly fatal lesion by inoculation of the peritoneal cavity with many of the standard cultures. Frequently one produces typical fibrinopurulent peritonitis, which, however, does not result fatally, whereas on the other hand, as the result of excessively large doses of bacteria the animal may succumb and the peritoneal cavity at necropsy exhibit none of the morbid changes characteristic of peritonitis.

On the basis of Steinberg's [2] extensive experiences, in which he was successful in producing peritonitis by intraperitoneal inoculation with the colon bacillus suspended in tragacanth, we have adhered to this method of producing experimental peritonitis. In the present study we have used his culture Bacillus coli no. 300, employing twenty-four hour agar cultures.

This paper reports the results of our more recent experiments concerning quantitative determinations of the peritoneal immunity which results from various abdominal operations.

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1. Coller, F. A., and Brinkman, H.: Studies on the Reaction of the Peritoneum to Trauma and Infection, Ann. Surg. **109**:942 (June) 1939.

2. Steinberg, B.: Experimental Background and Clinical Application of B. Coli and Gum Tragacanth Mixture (Coli Bactragen), Am. J. Clin. Path. **6**:253-277 (May) 1936.

The quantity of culture material used for the inoculation is designated in terms of slants of twenty-four hour agar cultures, the dose ranging in most instances from one fourth of a slant to two slants. According to careful calculations, the washings from one slant were estimated to contain approximately 5,000,000,000 organisms.

TABLE 1.—*Determination of Minimum Lethal Dose*

Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
663	Control	1/20 slant	Recovered	2 hr.	+	0	99	1	15,000
				4 hr.	0	0	97	3	19,000
				24 hr.	0	0	97	3	30,000
664	Control	1/20 slant	Recovered	2 hr.	No fluid obtained				
				4 hr.	+	0	98.2	1.8	12 000
				24 hr.	0	0	97.1	2.9	21,000
665	Control	1/10 slant	Recovered	2 hr.	No fluid obtained				
				4 hr.	+	0	97	3	9,000
				24 hr.	0	0	98	2	23 000
667	Control	1/ 5 slant	Recovered	2 hr.	0	0	98.6	1.4	6 500
				4 hr.	+	0	98.3	1.7	8,100
				24 hr.	0	+	97.1	2.9	33,000
684	Control	¼ slant	32 hr.	4 hr.	+	0	96	4	6,900
				24 hr.	+++	6	86	14	30,000
				32 hr.	++++	0	77	23	34,000
690	Control	¼ slant	Recovered	4 hr.	+	0	91	9	23,000
				24 hr.	0	0	82	18	150,000
				48 hr.	0	0	95	5	224,000
696	Control	¼ slant	Recovered	4 hr.	+	0	94	6	Fluid insufficient
				24 hr.	0	0	98	2	112,000
				48 hr.	0	0	97	3	73,000
669	Control	¼ slant	Recovered	4 hr.	+	0	97	3	31,000
				24 hr.	0	0	96	4	50,000
				48 hr.	0	0	95	5	42,000
				96 hr.	0	0	98	2	Fluid insufficient
668	Control	½ slant	8 hr.	4 hr.	++	0	94	6	21,000
				8 hr.	+++	0	82	18	60,000
691	Control	½ slant	10 hr.	1 hr.	+	+	89	11	4,600
				4 hr.	+	+	76	24	34,000
				10 hr.	+++	0	64	26	39,000
688	Control	½ slant	17 hr.	2 hr.	++	0	90	10	5,800
				4 hr.	+	0	81	19	14,400
				17 hr.	++++	0	89	11	24,000
673	Control	1 slant	46 hr.	4 hr.	++	+	76	24	9,100
				8 hr.	++	0	80	20	9,800
				24 hr.	++	0	54	46	63,000
				46 hr.	++++	0	60	40	51,000

METHOD AND RESULTS

Determination of the Minimum Lethal Dose of B. Coli.—The first problem was to determine the minimum lethal dose of B. coli for the normal dog. In the first experiment the following doses of the colon bacillus were given intraperitoneally: 1/20, 1/10, 1/5, ¼, ½, 1 and 2 slants. After the inoculation, peritoneal fluid was removed at various intervals by means of a fine capillary pipet. The total cell count of the fluid was determined, as was the percentage of polymorphonuclear leukocytes and large mononuclear cells. The relative number of free organisms in the fluid was estimated at these different times. The findings are shown in table 1. It was found that a dose of one-half slant was almost

invariably fatal, while a smaller dose was not. Doses larger than one-half slant were always fatal.

One half of one slant having been established as the minimum lethal dose for the normal dog, various abdominal operations, presently to be described, were performed.

Effect of Abdominal Operations on the Peritoneum.—In order to determine whether a surgical operation gives protection against subsequently induced peritonitis, two criteria were used. The first was the survival or death of the animal, a rather crude but nevertheless convincing method. It was not sufficiently precise, however, to indicate finer gradations of protection. The second, more delicate index was determination of the cellular response as well as of the relative number of free organisms in the peritoneal exudate.

Because of the prevailing belief that a colostomy affords considerable protection against peritonitis from subsequent operations, the effect of a colostomy on the

TABLE 2.—*Inoculation Two Weeks After End Colostomy*

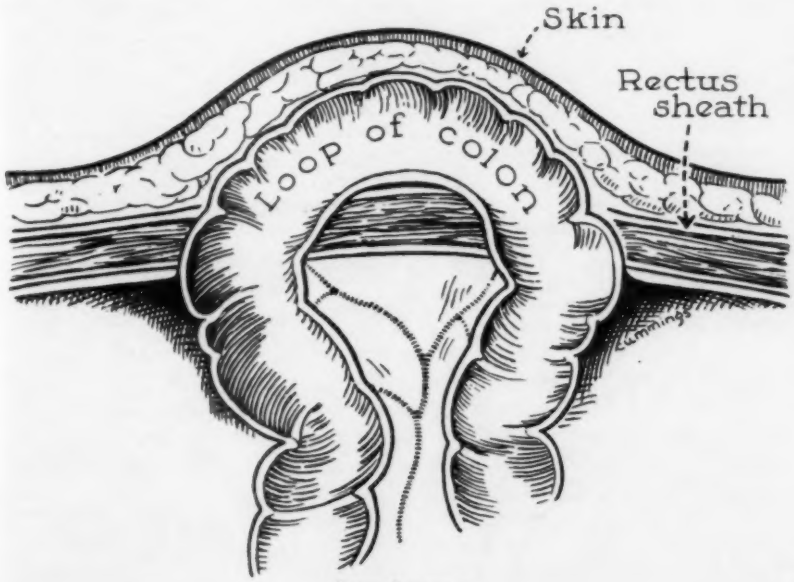
Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
722	End colostomy	¼ slant	18 hr.	Post mortem	++	0	88	12	298,000
719	End colostomy	¼ slant	Recovered	24 hr.	0	0	97	3	312,000
720	End colostomy	½ slant	11 hr.	Post mortem	+	0	90	10	284,000
700	End colostomy	½ slant	7 hr.	Post mortem	+++	+	84	16	140,000
704	End colostomy	1 slant	10 hr.	Post mortem	++	+	85	15	220,000
716	End colostomy	1 slant	6 hr.	Post mortem	+	0	90	10	234,000
666	Control	¼ slant	Recovered	24 hr.	+	0	98	2	122,000
688	Control	½ slant	17 hr.	Post mortem	++++	0	89	11	24,000

peritoneum was first studied. Six healthy dogs were selected and end colostomies performed in the routine manner, the distal portion of the colon being used. The animals were allowed to convalesce for two weeks, at the end of which time peritonitis was induced, doses of ¼, ½ and 1 slant respectively being given to each of 2 dogs. Two normal dogs were used as controls. The results of these experiments are given in table 2. It will be noted that only 1 of the colostomized dogs, 1 that received only one fourth of a slant (less than the minimal lethal dose), recovered. As compared with the controls, the important findings in the peritoneal fluid of these animals were: (1) a markedly increased number of leukocytes within a few hours after the inoculation and (2) a definitely smaller number of free organisms. The polymorphonuclear leukocyte was found to be the predominant cell in the exudate. From these experiments we concluded that the peritoneum showed no evidence of greatly increased resistance to infection two weeks after the establishment of a colostomy. However, judging from the increase in leukocytes in the peritoneal cavity and the small number of free organisms, we felt that there was some tendency toward protection.

In order to determine whether the degree of protection was dependent on the interval between operation and the production of peritonitis, colostomies

TABLE 3.—*Inoculation One Month After End Colostomy*

Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
737	End colostomy	¼ slant	Recovered	2 hr.	+	+	90	10	3,800
723	End colostomy	½ slant	6 hr.	Post mortem	++	0	88	12	96,000
721	End colostomy	1 slant	8 hr.	Post mortem	+++	0	93	7	128,000
718	End colostomy	2 slants	5½ hr.	Post mortem	+++	0	91	9	132,000
738	Control	¼ slant	Recovered	2 hr.	+	+	96	4	4,100
740	Control	½ slant	9 hr.	Post mortem	+++	0	62	36	212,000



Precolostomy

were again performed and peritonitis similarly produced at the end of four weeks. With this longer interval no greater protection was obtained (table 3).

In order to determine the reaction of the peritoneum to purely mechanical irritation in instances in which there is no factor of fecal contamination, further experiments were undertaken by means of the operation illustrated. A laparotomy was performed, and a segment of the distal part of the colon approximately 8 cm. long was drawn through the incision and implanted subcutaneously. For convenience this operation is referred to as a precolostomy. Such an operation was performed on each of 8 dogs. Again at the expiration of two weeks, peritonitis was induced by intraperitoneal inoculation with varying doses of colon bacillus (table 4).

It will be noted from a study of this table that there was evidence of considerable protection in this group. Both dogs receiving the minimum lethal dose recovered. Also, 1 that received two times and another that received four times the minimum lethal dose survived. It is of interest that in 1 instance (dog 678) in

which the implanted loop slipped back into the peritoneal cavity five days after operation the animal died, whereas dog 680, which received an equal dose, recovered. Once more it was observed that in this entire group of animals as compared with the controls the peritoneal fluid contained a large number of leukocytes but few extracellular organisms.

Furthermore, in the dogs which recovered there was a higher percentage of polymorphonuclear leukocytes than in the control dogs, emphasizing the importance of this cell in phagocytosis.

TABLE 4.—*Inoculation Two Weeks After Precolostomy*

Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
668	Control	½ slant	8 hr.	4 hr.	++	0	94	6	21,000
				8 hr.	+++	0	82	18	60,000
673	Control	1 slant	46 hr.	4 hr.	++	+	76	24	9,100
				8 hr.	++	0	80	20	9,800
				24 hr.	++	0	54	46	63,000
				46 hr.	++++	0	60	40	51,000
674	Precolostomy	¼ slant	Recovered	4 hr.	+	+	99	1	368,000
				24 hr.	0	0	97	3	536,000
				48 hr.	0	0	93	7	530,000
				96 hr.	No fluid obtained				
677	Precolostomy	¼ slant	Recovered	4 hr.	0	++	96	4	352,000
				24 hr.	0	0	94.8	5.2	314,000
				48 hr.	0	0	95	5	284,000
				96 hr.	No fluid obtained				
681	Precolostomy	½ slant	Recovered	4 hr.	+	0	97	3	390,000
				24 hr.	0	+	94.8	5.2	420,000
				48 hr.	0	0	92.3	7.7	431,000
				96 hr.	0	0	93.2	6.8	418,000
682	Precolostomy	½ slant	Recovered	4 hr.	+	+	98	2	402,000
				24 hr.	0	+	95.1	4.9	52,000
				48 hr.	0	0	94.6	5.4	480,000
				96 hr.	0	0	92.7	7.3	362,000
675	Precolostomy	1 slant	24 hr.	4 hr.	++	0	94.3	5.7	320,000
				24 hr.	++++	0	81	19	630,000
679	Precolostomy	1 slant	Recovered	4 hr.	0	++	97.5	2.5	528,000
				24 hr.	0	0	97.6	2.4	464,000
				48 hr.	0	0	93.7	6.3	614,000
				96 hr.	0	0	92.5	7.5	596,000
680	Precolostomy	2 slants	Recovered	4 hr.	0	+	93.5	6.5	304,000
				24 hr.	0	++	96.0	4.0	292,000
				48 hr.	0	+	97.6	2.4	214,000
				96 hr.	0	0	95.4	4.6	210,000
678	Precolostomy	2 slants	23 hr.	4 hr.	+	0	90	10	524,000
				23 hr.	++++	0	81	19	316,000

Having found this evidence of a fairly marked protection as the result of precolostomy, we selected an additional group of 10 dogs. Precolostomies were performed in a similar fashion. However, in this group of animals, instead of inducing peritonitis two weeks after the operation, we simply opened the subcutaneous colostomy at this time, producing an artificial anus in the abdominal wall. Two weeks after the opening of the loop peritonitis was induced. The results are shown in table 5. Contrary to our expectations, there was considerably less evidence of protection in these animals than in those in which the loop had been left intact. In fact, there was actually less evidence of protection than in normal dogs. The 2 dogs that received ¼ slant died, whereas the normal dog will tolerate a dose of this size. The peritoneal exudate again showed some increase in the number of leukocytes. In an attempt to rationalize these results

TABLE 5.—*Inoculation Two Weeks After Opening Colostomy (One Month Postoperatively)*

Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
696	Opened precolostomy	¼ slant	18 hr.	Post mortem	+	+	89	11	180,000
697	Opened precolostomy	¼ slant	20 hr.	Post mortem	++	0	84	16	130,000
701	Opened precolostomy	½ slant	22 hr.	Post mortem	++	0	75	25	212,000
695	Opened precolostomy	1 slant	7½ hr.	Post mortem	+	+	79	21	114,000
699	Opened precolostomy	1 slant	6 hr.	Post mortem	+	+	84	16	59,000
705	Opened precolostomy	1 slant	18 hr.	Post mortem	++	0	90	10	58,000
710	Opened precolostomy	1 slant	21 hr.	Post mortem	++	0	87	13	32,000
709	Opened precolostomy	2 slants	5 hr.	Post mortem	++	+	80	20	48,000
670	Opened precolostomy	½ slant	8 hr.	Post mortem	+++	+	88	12	29,000
671	Opened precolostomy	½ slant	6 hr.	Post mortem	++++	+	95	5	42,000
689	Control	¼ slant	Recovered	8 hr.	+	0	91	9	16,000
691	Control	½ slant	10 hr.	Post mortem	++++	+	83	17	5,900

TABLE 6.—*Inoculation Four Days After Removal of Peritoneum* *

Dog No.	Procedure	Dose	Survival Time	Time of Smear	Relative Number Free Organisms	Phagocytosis	Polymorphonuclears, %	Mononuclears, %	W.B.C. (Peritoneal Fluid)
729	Removal of peritoneum	2 slants	Recovered	4 hr.	+	+	92	8	312,000
				24 hr.	0	0	92	8	490,000
730	Removal of peritoneum	2 slants	Recovered	4 hr.	0	++	95	5	514,000
				24 hr.	0	0	97	3	620,000
731	Removal of peritoneum	2 slants	Recovered	4 hr.	0	+	98	2	600,000
				24 hr.	0	+	98	2	584,000
732	Removal of peritoneum	2 slants	Recovered	4 hr.	0	+	89	11	426,000
				24 hr.	0	0	95	5	590,000
734	Removal of peritoneum	2 slants	Recovered	4 hr.	+	++	92	8	420,000
				24 hr.	0	0	96	4	598,000
725	Removal of peritoneum	2 slants	20 hr.	4 hr.	+	+	94	6	396,000
				20 hr	++++	0	87	13	328,000
726	Removal of peritoneum	2 slants	18 hr.	4 hr.	+	+	90	10	490,000
				18 hr.	+++	0	84	16	478,000
771	Control	2 slants	Recovered	4 hr.	++	+	91	9	484,000
				24 hr.	0	0	97	3	612,000
772	Control	2 slants	Recovered	4 hr.	+	+	95	5	530,000
				24 hr.	0	0	98	2	580,000
				48 hr.	0	0	97	3	514,000

* Coli bactragen two days after operation.

it might be suggested that the increase in the interval between the operation and the production of peritonitis was significant. Thus it seems probable that the protection derived from the laparotomy is largely lost after such a long interval. We found this to be true also in earlier experiments reported in a previous communication. It was not our impression that the decreased protection was due to malnutrition or to any debility resulting from the colostomy.

Effect of Partial Removal of Peritoneum on Vaccination.—In view of the fact that it is often necessary in certain abdominal operations to remove large areas of peritoneum, experiments were planned to investigate the effect of such a procedure on vaccination. The operation consisted in removal of a large portion of the parietal peritoneum from both sides of the abdominal wall. The incision extended the entire length of the abdomen, and the parietal peritoneum was removed as far posteriorly as the vertebral column. Slight hemorrhage was encountered, and the wounds healed by primary union. Two days after removal of the peritoneum as described an attempt was made to produce hyperleukocytosis by the injection of coli-bactragen into the abdominal cavity. It has been shown repeatedly by Steinberg that this method of producing peritoneal leukocytosis is practically infallible in the normal dog. It has also been demonstrated by him that such a leukocytic response affords marked protection against subsequently induced peritonitis. Two days after the administration of the coli-bactragen or four days after operation peritonitis was induced, living cultures of the colon bacillus in large doses being used. The results are shown in table 6, and it will be noted that the 2 controls recovered, as did 5 of the 7 dogs. In all of the animals, both controls and those with a portion of the peritoneum removed, there was a consistently high leukocyte count in the peritoneal fluid. There was a marked predominance of polymorphonuclear leukocytes in the dogs which recovered, this predominance being less marked in the animals which died. It was our conclusion that even in the absence of a fairly large portion of the peritoneum a greater protection was afforded by this method of peritoneal vaccination than was obtained by any of the operations described.

COMMENT

If these experimental studies may be applied to the human patient, it would seem on the basis of peritoneal "immunity" alone that there is little argument in favor of operation in stages. Other factors, however, which may be of greater importance than that of immunity, must be seriously considered, and the experimental studies presented here are not to be interpreted as a condemnation of multiple stage operations. Undoubtedly the formation of adhesions, with the walling off of definite compartments within the peritoneal cavity, is an important function of the peritoneum which helps to prevent general peritonitis at subsequent operations. Of significance also is the fact that in multiple stage operations the function of a colostomy or intestinal anastomosis becomes well established prior to the resection, whereas otherwise the physiologic adjustment of the intestinal tract to this alteration is superimposed on a major surgical procedure.

When complicating factors, such as obstruction, perforation or abscess formation are present, the necessity for stage operations is quite evident.

Finally, the lessened trauma from a smaller operation may be desirable for the debilitated patient.

We appreciate the fact that these studies have not given the final answer to many of the controversial questions which arise in dealing with peritonitis, but we hope that they will serve to stimulate further investigation along these lines.

CONCLUSIONS

Under the conditions of the foregoing experiments it seems that abdominal operations confer on the peritoneum some degree of resistance to infection. This resistance is not marked, however, and is less than that which can be obtained by intraperitoneal vaccination. The protection derived from operation was of short duration, being uniformly less at the end of one month than at the end of two weeks after operation. The greatest degree of protection was observed after subcutaneous implantation of an unopened loop of colon (precolostomy), in which there was no factor of infection other than that incidental to an exploratory laparotomy. Removal of a large portion of peritoneum had little if any effect on the mobilization of leukocytes in the abdominal cavity after intraperitoneal vaccination (coli-bactragen). Careful microscopic examination of the peritoneal fluid at varying intervals after the production of peritonitis revealed that the polymorphonuclear leukocyte was the important cell as far as phagocytosis was concerned.

STAGES IN PERITONITIS BASED ON THE DEFENSE MECHANISM IN RELATION TO TREATMENT

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TOLEDO, OHIO

Peritonitis is an inflammatory process similar in its fundamental character to inflammation elsewhere in the body but modified by the functional activities peculiar to the peritoneum. Absorption of diffusible bacterial toxins, passage of bacteria, omental migration and intestinal motor activity are some of the pertinent processes which determine the outcome of peritoneal inflammation. The nature of the invading bacteria and the host's protective response supply most of the variable factors which modify the course of the disease. Since inflammation is essentially a defense measure, the local lesion of the peritoneum is necessarily a protective mechanism. The systemic effects may be considered results of the struggle between the infecting bacteria and the host.

In order to evaluate the relative significance of the factors in peritonitis, it is essential to determine the histologic progression of the disease, the progressive exudative changes and the nature of the damage to the host. It is obvious that within the space allotted neither experimental investigations nor clinical correlations can be detailed; hence, only a summary of conclusions is presented.

NATURE OF THE DEFENSE MECHANISM

Polymorphonuclears constitute the most important factor in the local struggle.[1] Probably there are additional elements, such as fibrin, opsonins, and other antibodies, which may or may not play some part in the defense. The role of these elements is considered negligible except in certain conditions of bacterial invasion, such as pneumococcic infection. Shortly after the onset of peritonitis, the circulating polymorphonuclears show an appreciable drop in numbers. This drop coin-

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From the Department for Medical Research, Toledo Hospital.

Read before the Section on Surgery, General and Abdominal, at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 17, 1939.

1. (*a*) Steinberg, B., and Snyder, D. A.: Immune Cellular Reactions in Experimental Acute Peritonitis, Arch. Path. **8**:419 (Sept.) 1929. (*b*) Nylander, P. E. A.: Inflammatory Reaction in the Omentum, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:453, 1933.

cides with the appearance of leukocytes in the peritoneal exudate.[2] The next phase in the leukocytic picture is the surrender of the leukocytes by the tissue reservoirs.[3] Owing either to some stimulating factor or factors or to withdrawal of leukocytes from the circulation and tissue depots, the tempo of bone marrow activity is accelerated and more leukocytes are poured into the circulation. These cells eventually find their way into the peritoneal cavity. The peritoneal exudate reveals rapid

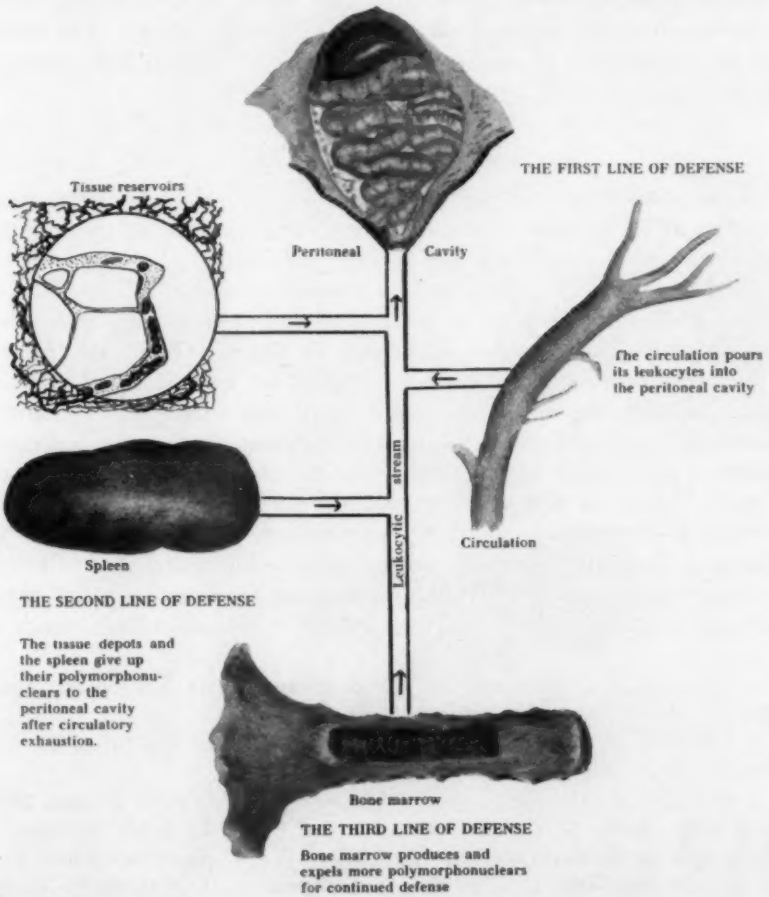
THE FIRST LINE OF DEFENSE
Tissue reservoirs
Peritoneal Cavity
The circulation pours its leukocytes into the peritoneal cavity
Circulation
Leukocytic stream
Spleen
THE SECOND LINE OF DEFENSE
The tissue depots and the spleen give up their polymorphonuclears to the peritoneal cavity after circulatory exhaustion.
Bone marrow
THE THIRD LINE OF DEFENSE
Bone marrow produces and expels more polymorphonuclears for continued defense

Fig. 1.—Defense mechanism against peritonitis. It is shown to consist of mobilization and migration of polymorphonuclears into the peritoneal cavity.

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2. Pons, C. A.; Gannon, J. M., and Belk, W. P.: Withdrawal Aleukocytosis in Experimental Peritonitis, Am. J. Clin. Path. **5**:225 (May) 1935. Steinberg and Snyder.[1a]

3. Gohrbandt, P.: Experimental Investigations on Spleen Changes in Peritonitis, Virchows Arch. f. path. Anat. **272**:783, 1929.

phagocytosis by the polymorphonuclears of the invading bacteria. This ingestion is complete within a very short period. Survival is invariably associated with complete removal of bacteria. Death, on the other hand, is consistent with a gradually increasing number of free peritoneal bacteria and with polymorphonuclear insufficiency.[4] An experiment may be cited to demonstrate the role of the polymorphonuclears. When leukocytes produced in one animal are injected into the peritoneal cavity of another animal with otherwise lethal peritonitis, the subject survives and shows complete phagocytosis of the bacteria.[5] The defense may be summarized as consisting of rapid and sufficient mobilization of polymorphonuclears in the peritoneal cavity.

INHIBITORY MECHANISM

Absorption from the peritoneal cavity is probably one of the more pertinent of the processes which determine the outcome of the infection. Absorption is accomplished through the medium of the lymphatic vessels and the serosal capillary bed.[6] There is considerable evidence that bacteria choose the lymphatics for a principal pathway and that soluble toxic substances are carried off largely by the capillaries. It must be emphasized, however, that both the capillaries and the lymphatics are capable of removing either the larger, particulate bacteria or the smaller, crystalloid bacterial toxic substances.[7] Inflammation of the peritoneum alters the mechanism of removal of contaminants from the peritoneal cavity.[8] When the inflammatory process persists for a certain period, removal of bacteria is markedly diminished, and the relatively few micro-organisms that escape do so through the lymphatic channels.[9] On the other hand, soluble, diffusible substances, such as bacterial toxins, continue to be absorbed.[10] These soluble toxic substances reach the

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4. Steinberg, B.: A Rapid Method of Protecting the Peritoneum Against Peritonitis, Arch. Surg. **24**:308 (Feb.) 1932.

5. Steinberg, B.: Transfer of Living Leukocytes and the Effect on Acute Infectious States, Arch. Path. **25**:785 (June) 1938.

6. Bolton, C.: Absorption from Peritoneal Cavity, J. Path. & Bact. **24**:429 (Oct.) 1921. Wells, H. G., and Johnstone, O. P.: On the Route of Absorption of Bacteria from the Peritoneal Cavity, J. Infect. Dis. **4**:582 (Nov.) 1907. Steinberg, B., and Goldblatt, H.: Studies on Peritonitis: II. Passage of Bacteria from the Peritoneal Cavity into Lymph and Blood, Arch. Int. Med. **39**:449 (March) 1927.

7. Buxton, B. H., and Torrey, J. C.: Studies in Absorption, J. M. Research **15**:3, 1906.

8. Miller, R. G.: The Influence of Inflammation on the Absorption of Substances of Varied Diffusibility, J. Exper. Med. **67**:619 (April) 1938.

9. David, V. C.: Peritonitis: Experimental Study, Surg., Gynec. & Obst. **45**:287 (Sept.) 1927.

10. Steinberg, B.: The Cause of Death in Acute Diffuse Peritonitis, Arch. Surg. **23**:145 (July) 1931.

various viscera and induce damage. The myocardium, because of the nature of the heart, is perhaps the most important structure so affected.[11] An experiment demonstrates the mechanism just described. Introduction of a homologous antiserum or an antitoxin into an experimental animal with diffuse peritonitis results in survival providing administra-

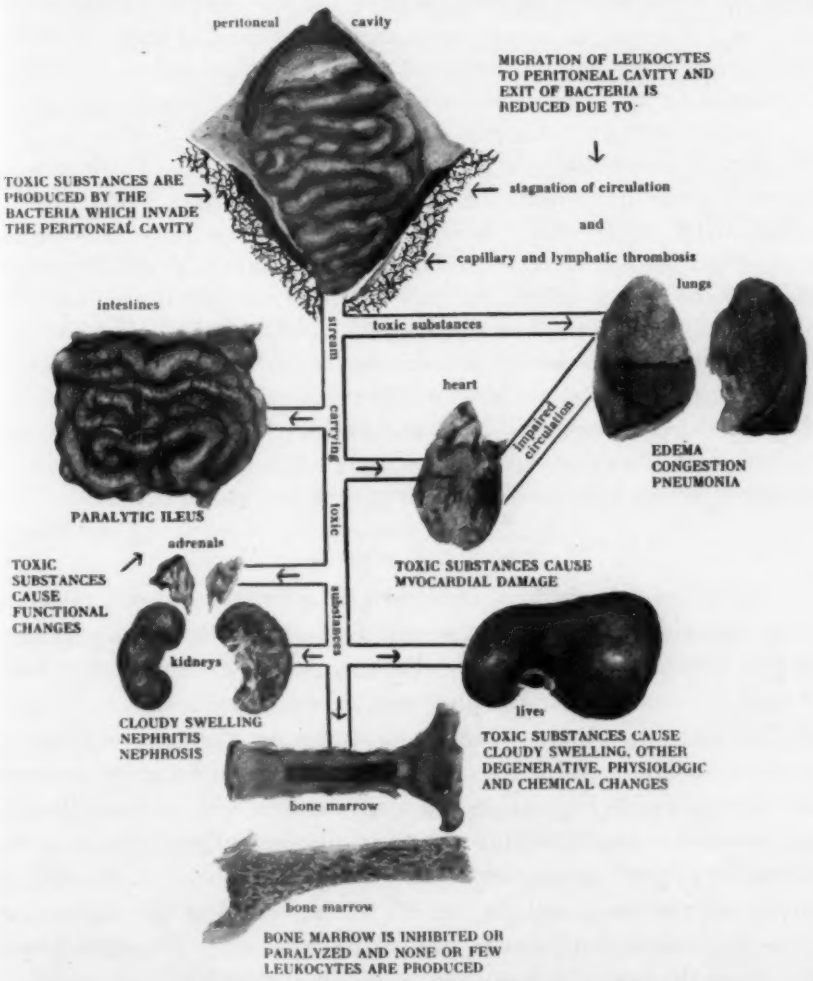

Fig. 2.—Inhibitory mechanism in the defense against peritonitis.

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11. Steinberg, B.; Kobacker, J. L., and Russell, T. G.: Cardiovascular System in Acute Experimental Peritonitis, Proc. Soc. Exper. Biol. & Med. **30**:1155 (May) 1933. Steinberg, B., and Kobacker, J. L.: The Cardiovascular System in Protected and Unprotected Animals with Acute Diffuse Peritonitis, J. Lab. & Clin. Med. **20**:1180 (Aug.) 1935.

tion is done prior to irreversible myocardial damage.[10] Evidences of the effects on the heart of the toxic substances are deduced from studies of electrocardiographic tracings and determinations of continuous blood pressure during the course of peritonitis.[11b]

The histologic progressive changes of the peritoneal tissue result from the effect of the invading bacteria and the reaction on the part of the host. After onset of peritonitis, there is a period of bacterial inactivity corresponding to the "bacterial lag," an adaptation of the microorganisms to the new environment. The inflammatory process during this period is slight. Bacteria pass from the peritoneal cavity into the circulation, and leukocytes enter the cavity. After the bacteria adapt themselves to the peritoneum, they begin to multiply and induce an inflammation of a greater degree. There are consequent slowing and (later) stagnation of the circulation, with capillary and lymphatic thrombosis. As a result, the rate of bacterial passage is markedly diminished, and by the same token polymorphonuclears enter the peritoneal cavity in considerably smaller numbers. After a certain interval the bacteria begin to produce soluble toxic substances which diffuse through the peritoneum to reach the various viscera. When the time of action of the toxic substance is sufficiently prolonged, the visceral damage becomes irreversible and permanent, and death ensues.

STAGES IN PERITONITIS

On the basis of the local peritoneal struggle, the systemic responses to the infection and the protective and inhibitory mechanisms, peritonitis may be divided into three stages. Each stage can be interpreted in terms of both the local peritoneal change and the systemic effects.

The first (primary) stage lasts for approximately eighteen to twenty-four hours and corresponds to the period of bacterial inactivity and maximum efficacy on the part of the host's defenses. Bacteria are removed from the peritoneal cavity, and their destruction is accomplished by a threefold process: local peritoneal phagocytosis, bactericidal activity of the blood and the activity of the reticuloendothelial system. Since the peritoneal tissues are only slightly affected by the inflammatory process at this stage, polymorphonuclears enter the peritoneal cavity in large numbers and are available for phagocytosis of the bacteria. At this stage, enhancement of the host's defenses is indicated whenever they are found insufficient to cope with the infection. The primary stage may terminate with recovery when bacterial destruction is accomplished, or it may continue into the next (secondary) stage.

The secondary stage of peritonitis lasts from twelve hours to three days, depending on the virulence and the number of the invading bac-

teria and the degree of resistance [12] of the patient. The stage is initiated by a marked bacterial proliferation and sufficient inflammatory tissue changes of the peritoneum to interfere with bacterial passage and leukocytic migration. The defense mechanism of the body is at a low point, but artificial enhancement in the early period may aid in overcoming the infectious process. The local struggle is the only measure of defense in this stage. Destruction of bacteria terminates this stage, and failure of destruction of bacteria results in progression of the disease to the final (tertiary) stage.

The tertiary stage is characterized by the elaboration of bacterial toxic substances with their diffusion from the peritoneal cavity and their effect on the viscera. The stage lasts from twelve hours to three days, depending on the titer of the toxic substances and their quantitative neutralization by antibodies which may be harbored by the patient. The pertinent effects of the toxic substances are on the bone marrow and the myocardium. The activity of the one is inhibited or paralyzed, and serious circulatory impairment results from the action on the other. The host's defense mechanism is incapacitated. Treatment obviously should be directed toward neutralization of toxic substances and preservation of the integrity of the vascular system. The damage accomplished in the late tertiary stage is irreversible and irreparable.

DETERMINATION OF THE STAGES

Although clinical manifestations may furnish sufficient evidence for the establishment of the stages in peritonitis, a quantitative procedure is obviously more satisfactory. Correlation of experimental methods in various problems in peritonitis with clinical material established a relatively simple criterion for differentiation of the stages. Since repeated investigations indicated that the local peritoneal picture reflects the defensive and the inhibitory mechanisms of the host, the peritoneal exudate was utilized for determination of the stages. It was found that the number of free bacteria in the exudate constitutes a simple and reliable guide.[13] On this basis the stages are differentiated according to the number of free bacteria in an average field. The primary stage is characterized by the presence of six or less free bacteria. The phagocytosed micro-organisms are disregarded. The secondary stage is

12. Resistance is interpreted to include the activity of the bone marrow, leukocytic migration, a competent circulatory system and a ready response on the part of the reticuloendothelial system.

13. Steinberg, B.: Peritonitis, to be published.

denoted by the presence of six to ten free bacteria, and the tertiary stage, by more than ten free micro-organisms.

The exudate may be obtained either at operation or by abdominal puncture. The time consumed by the technical details should not exceed

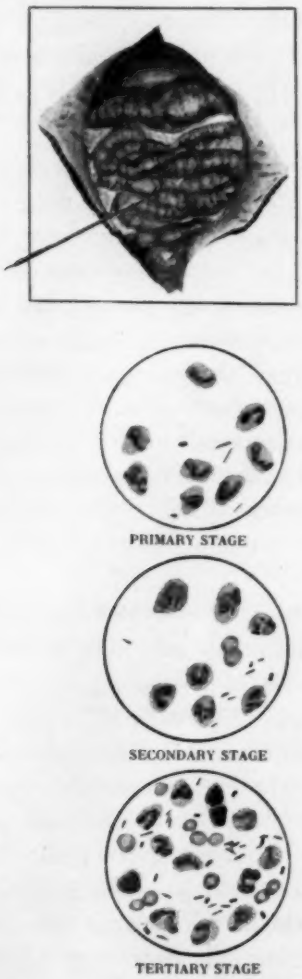

Fig. 3.—Determination of the stages of peritonitis.

a few minutes. Smears are stained with Wright's and Gram's stains, the free bacteria are counted in ten fields and an average in one field is calculated. Such a rapid determination of the stage offers a visual picture of the relative state of the defensive and inhibitory mechanisms of the patient and allows the choice of treatment.

TREATMENT IN RELATION TO THE STAGES

Since the primary and the early part of the secondary stage of acute diffuse peritonitis allow the normal defenses of the host to be mobilized against bacterial invasion, the defense may be enhanced by artificial means. During this period, mobilization of polymorphonuclears in the peritoneal cavity is unrestricted by the physical changes apparent later in inflammation. Since these leukocytes constitute the essential element in the defense, any procedure which stimulates their production and accomplishes their local mobilization should be utilized. Experimental

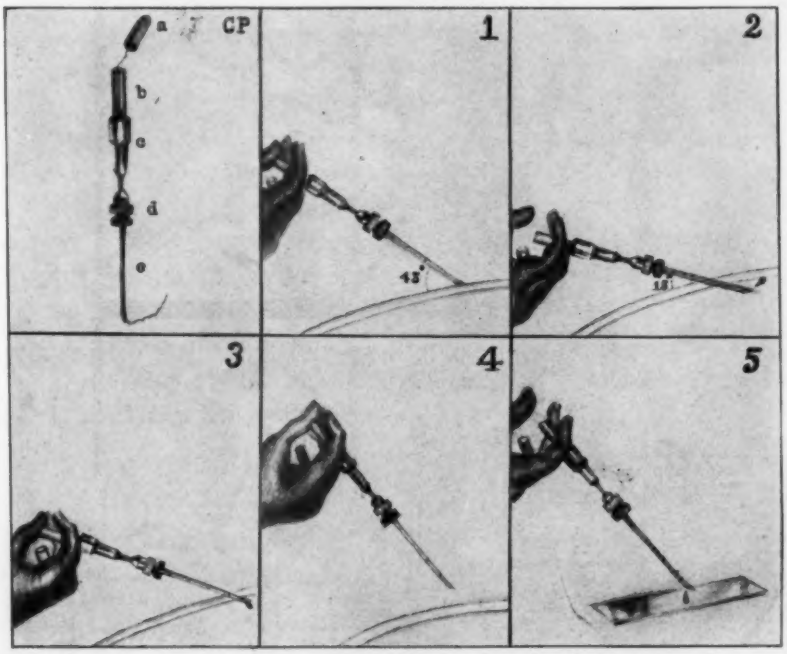

Fig. 4.—Method of testing. *CP*, capillary pipet for obtaining small volumes of peritoneal exudate by abdominal puncture. Note (*a*) rubber cap, (*b*) capillary glass pipet, (*c*) steel or silver capillary, (*d*) movable guard and (*e*) 2 inches (5 cm.) of a graduated capillary needle. *1*, introduction of the needle through the abdominal wall with the thumb covering the lumen of the glass capillary so as to prevent blood from entering the needle during its passage through the abdominal wall. *2*, removal of the thumb while the needle is laid down to form an angle of 15 degrees between the shaft and the abdominal wall. *3*, attraction of peritoneal exudate to the capillary bore (capillary attraction). *4*, exudate filling the glass capillary. The thumb is placed over the capillary, and the needle is drawn out. *5*, expulsion of a drop of the exudate on a glass slide.

investigations and clinical applications have demonstrated that introduction into the peritoneal cavity of a satisfactory "leukocyte stimulating and mobilizing substance" suspended in tragacanth accomplished those

purposes.[14] Later in the secondary stage, with inhibition of the host's defensive measures, such stimulation is obviously of little or no value. Treatment should be directed to conserving the circulatory system, stimulating the bone marrow and aiding phagocytosis in the peritoneal cavity by the available leukocytes. These purposes may be accomplished indirectly by complete rest, administration of morphine and

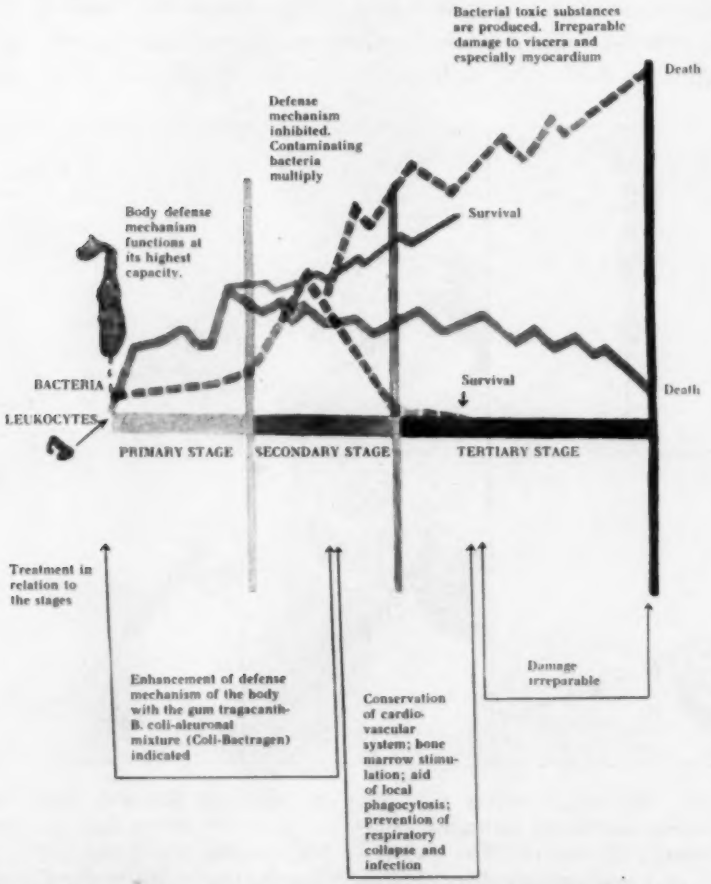
Bacterial toxic substances are produced. Irreparable damage to viscera and especially myocardium
Death
Defense mechanism inhibited. Contaminating bacteria multiply
Body defense mechanism functions at its highest capacity.
Survival
BACTERIA
LEUKOCYTES
Survival
Death
PRIMARY STAGE
SECONDARY STAGE
TERTIARY STAGE
Treatment in relation to the stages
Enhancement of defense mechanism of the body with the gum tragacanth-B. coli-aleuronat mixture (Coli-Bactragen) indicated
Conservation of cardio-vascular system; bone marrow stimulation; aid of local phagocytosis; prevention of respiratory collapse and infection
Damage irreparable

Fig. 5.—Schematic representation of the stages in peritonitis in relation to the defense mechanism and to treatment.

avoidance of any additional intestinal motor excitants. Administration of oxygen, with frequent periods of inhalation of carbon dioxide (to pre-

14. Steinberg, B.: An Improved Method of Protecting the Peritoneum of Dogs Against Fatal Colon Bacillus Infection, Proc. Soc. Exper. Biol. & Med. **29**: 1018 (May) 1932. Steinberg, B., and Goldblatt, H.: Protection of Peritoneum Against Infection, Surg., Gynec. & Obst. **57**:15 (July) 1933. Steinberg, B.: The Experimental Background and the Clinical Application of the Escherichia Coli and Gum Tragacanth Mixture (Coli-Bactragen) in Prevention of Peritonitis, Am. J. Clin. Path. **6**:253 (May) 1936.

vent bronchial occlusion and pneumonic lesions), and daily small blood transfusions serve further to accomplish the desired effects. Since water and food cannot be taken by mouth, these substances should be administered by intravenous introduction of not over 3,000 cc. of physiologic solution of sodium chloride and 500 cc. of 10 per cent dextrose a day except in the presence of vomiting, when additional fluid should be given.[15] Sodium chloride and dextrose should be administered cautiously.[16] Excessive administration of sodium chloride and fluid will result in increase of peritoneal fluid [17] and a greater effort for an already damaged heart. Treatment of the tertiary stage may follow that of the secondary, but, although much can be done, little will be accomplished. The damage produced by the toxic substances in the late tertiary stage is irreparable.

SUMMARY

1. Peritonitis is divided into three stages. The division is based on the defensive and inhibitory mechanisms of the host.

2. The various factors operating in defense of the host against invasion by bacteria are enumerated. The inhibitory factors which militate against recovery are placed in their relation to the local and systemic changes.

3. A method of differentiation of stages is described.

4. Treatment of the various stages is associated with the defense and the inhibitory mechanisms.

ABSTRACT OF DISCUSSION ON PAPERS BY DRS. COLLER, RANSOM AND RIFE AND DR. STEINBERG

DR. F. A. COLLER (Ann Arbor, Mich.): The peritoneum is an enormous serous surface that roughly approximates the surface area of the skin. It has an excellent blood and lymphatic supply and a generous supply of omentum, apparently designed for protection against bacterial and traumatic injury.

Infection of the peritoneum is occasionally primary but commonly secondary to infection originating in abdominal viscera. Formerly the peritoneum was opened with fear because it was thought that its resistance was low. More recently there has been ascribed to it a specific immunity that can be increased by the use of various vaccines. Dr. Steinberg has put forward a new conception of protection against infection through the production of local hyperleukocytosis artificially or through the reaction of the peritoneum to trauma and infection. His experimental work has shown that artificial production of hyperleukocytosis will protect against subsequently induced peritonitis.

15. Maddock, W. G., and Coller, F. A.: Water Balance in Surgery, J. A. M. A. **108**:1 (Jan. 2) 1937.

16. Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, J. A. M. A. **107**:1522 (Nov. 7) 1936.

17. Blalock, A.: Effect of the Administration of Salt Solution on the Amount of Fluid That Accumulates in the Peritoneal Cavity, Arch. Surg. **26**:1098 (June) 1933.

Our work, like this, may be criticized as dealing with peritonitis produced by a single organism when we know that in clinical peritonitis there are many types of bacteria at work. However, we have used a certain strain of B. coli so that we could have a dose of bacteria that was lethal with a constant dosage. Dr. Steinberg has demonstrated that phagocytosis is the important local reaction and that any procedure such as the introduction of antiseptics or wiping the bowel to remove exudate interferes with this reaction and diminishes local resistance. This emphasizes the importance of minimizing manipulations in an abdomen which is the site of peritonitis.

One must emphasize the importance also of aid in maintaining all other physiologic activities of the body while the combat between the bacteria and the leukocytes is going on in the peritoneum.

The gastrointestinal tract must be kept at rest by prohibition of food, drink and cathartics. Distention, which decreases the vital capacity, must be combated by morphine and constant aspiration of the stomach and of the upper part of the small intestine. Dehydration, ketosis and hypochloration secondary to vomiting, aspiration and starvation must be corrected by proper administration of fluids. Anoxia due to distention, pulmonary complications or perhaps toxemia must be treated by oxygen therapy. Operative procedures must be limited to those that simply stop the infection at its source. One cannot overemphasize the importance of maintaining body function with these measures.

We have shown that trauma to the peritoneum produced by operation gives a small degree of protection against infection, but the immunity is not adequate to protect against severe degrees of infection.

In my experimental and clinical observations I find that the preliminary production of hyperleukocytosis does give protection against infection incurred at operation. However, in most operations, unless there is frank soiling of the peritoneum by operative mishap this protection is not necessary. If there is gross contamination, I now use a preparation of colon bacilli, aleuronat and tragacanth (coli-bactragen) at operation. In most operations I feel it is not necessary; nothing prevents postoperative peritonitis like careful, aseptic operative technic, and nothing aids the body in combating peritonitis after it is established like the maintenance of normal chemical and physiologic activity by use of the measures mentioned.

DR. C. F. DIXON (Rochester, Minn.): The work of Dr. Coller and his associates closely coincides with that of Hermann, carried out about eight years ago.

I realize that there are some who believe that the use of vaccine as a preoperative safeguard against peritonitis is of no value. Some have even gone so far as to state that the intraperitoneal injection of vaccine is a dangerous procedure. Many thousands of such injections have been carried out for patients in the intestinal service at the Mayo Clinic without the occurrence of untoward results. For some years I have been of the opinion that the incidence of peritonitis following surgical operations on the colon has been definitely decreased by this maneuver. The vaccine we of the clinic use is essentially the same as that advocated by Dr. Steinberg, except that, in addition to colon bacilli, streptococci are included in the preparation.

During the past year I have used vaccine in the treatment of alternate patients in my service for whom operations were performed on the colon and ileum. The study is not yet complete, but an accurate statistical evaluation by one of my associates, Dr. W. J. Tennison, has reached the stage at which some deductions can be drawn, and it depicts the fact that deaths from peritonitis were fewer among

patients to whom vaccine was administered. In considering patients on whom abdominoperineal anterior resection or so-called exteriorization operations were performed, the mortality in the hospital among the group of patients receiving vaccine was only 6 per cent as compared to 17 per cent for patients who were not vaccinated.

For patients in whom gross soiling occurs, I have in many instances used a preparation of colon bacilli, aleuronat and tragacanth (coli-bactragen), recommended by Dr. Steinberg.

Frequently the statement is heard: "If good technic is employed, peritonitis will rarely occur." It is of course assumed that the surgeon invariably attempts to do his best; however, peritonitis still occurs, and I think it develops much more often if vaccine is not employed.

It seems to me that a sufficient amount of investigation has already been done on this subject to warrant the use of vaccine as a possible preventive procedure against peritonitis.

DR. J. SHELTON HORSLEY (Richmond, Va.): Dr. Steinberg has done a splendid piece of work in developing his coli-bactragen and in investigation of the pathogenesis of peritonitis.

The coli-bactragen as now prepared, with formaldehyde-killed, instead of heat-killed Escherichia coli, is better than the earlier product because it attains maximum efficiency in a few hours and can be used at the time of operation. I use it consistently in operations on the colon or in any other operations in which peritonitis may be anticipated. It is, of course, not a panacea and cannot cure a leaking suture, but I am confident of its value and would not do without it.

The coli-bactragen itself is a preventive of peritonitis. It is not a treatment for well established peritonitis, but Dr. Steinberg's suggestion of producing leukocytes in one animal and injecting them into another may lead to a cure in developed peritonitis.

My two sons and I reported on 972 operations for appendicitis between Jan. 1, 1931, and May 1, 1939. There were 85 cases of perforated appendix with abscess and localized peritonitis and 34 cases of spreading or diffuse peritonitis. In the latter group only 1 patient died. There were six deaths in the whole series of 972 cases.

Since Jan. 1, 1931, we have adopted five points in the treatment of appendicitis. We have added the use of suction in every case of abscess or peritonitis. We never sponge or place gauze in the peritoneal cavity in such cases. Complete rest is given to the bowel by avoidance of proctoclysis and by administration of dextrose in Ringer's solution intravenously. Of course this is necessary only in case of abscess or peritonitis. The three points which we had been and are still stressing are: (1) immediate operation at any stage of appendicitis, (2) the McBurney incision and (3) simple ligation of the stump of the appendix.

DR. W. WAYNE BABCOCK (Philadelphia): With interest aroused by Dr. Steinberg's work, I have used coli-bactragen in a few cases and have seen unexpected recovery after heavy peritoneal contamination.

Unfortunately, in many cases one is as yet unable to increase the resistance of the body sufficiently to overcome the peritoneal infection. Three other factors in peritonitis should constantly be borne in mind. The first is the initial bacterial contamination, which, of course, is a chief concern of aseptic surgical practice. The second is the propagating factor—the blood, the necrotic tissue, the serum, the bile, the intestinal contents or the culture medium in which an otherwise harmless number of bacteria may multiply into an overwhelming horde and then swarm

through the cavity in numbers beyond the capacity of the phagocytes and other protective elements to destroy. Spreading peritonitis is a liquid-borne disease. The third factor is the serous or other fluid that carries the bacteria from one part of the peritoneal cavity to another. I have attempted, with encouraging results, to prevent the diffusion of bacteria within the peritoneal cavity by internal exteriorization. Large, open glass tubes (lamp chimney drains) are anchored over a localized abscess, necrotic tissue, a septic gallbladder, a gangrenous appendix or a questionable line of intestinal suture, so that evacuation may occur with the peritoneum protected by isolating adhesions.

I have also removed liquid culture medium and diffusing fluid from the abdominal cavity after operations in which bacterial contamination was feared by the use of aspirating or Sump drains. These are double tubes of glass, the outer tube perforated and the inner tube connected with a continuously acting aspirator pump. By these drains a relatively dry peritoneum may be maintained for several days. Differing from rubber and other drains now used, glass drains may remain in the human peritoneal cavity for several days without plastic exudate or adhesion. Therefore, drainage of the peritoneal cavity, heretofore often considered impossible, is feasible at least for two or three days provided that only glass drains are used. By constant attention to these four factors, diffuse peritonitis in many cases may be prevented or arrested.

DR. BERNHARD STEINBERG (Toledo, Ohio): I should like to reemphasize Dr. Coller's warning that the patient as a whole must be treated and not only a part of him, such as the peritoneal cavity. Limitation of time prevents stressing this important element in the original presentation.

I should like to emphasize also that the problem of peritonitis, which has been considered for many years only from the mechanical point of view, is also one of physiologic, chemical, bacteriologic and immunologic concern. It is therefore essential to recognize the nature and the scope of the role played by these factors in peritonitis.

PERITONITIS IN CATS PRODUCED BY INTRA-PERITONEAL INJECTION OF BACILLUS COLI SUSPENDED IN MUCIN

GABRIEL P. SELEY, M.D.
NEW YORK

Numerous attempts have been made to produce bacterial peritonitis in animals. In some experiments attempts were made to enhance the pathogenic effect of bacteria by preliminary treatment of the peritoneum of laboratory animals with a great variety of substances: turpentine (David [1]), agar (David and Loring [2]), croton oil (Pawlowsky [3]), potato (Halsted [4]), omental ligation (Halsted [4]), sarcolin (Solieri [5]), intestinal juices (Blalock [6]) and tragacanth (Benians; [7] Steinberg [8]).

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* Ralph Colp Fellow in Bacteriology.

From the Laboratories of the Mount Sinai Hospital

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(Footnote continued on next page)

In other experiments different inoculums were tried: feces (Herrmann [9]), fecal emulsions (Wilen and Dragstedt [10]) and contents of small intestines (Pawlowsky [3]). The intestinal tract has been employed as the source of peritoneal infection by ligation of the appendix (Costain; [11] Lehman [12]), division of the appendix (Blalock [13]), ligation of the mesoappendix (Blalock [13]), perforation or incision of the gastrointestinal tract at different levels (Bergh [14]) or drainage of an open loop of ileum into the peritoneal cavity (Buchbinder [15]). Mucin has been found of definite value in increasing the virulence of induced bacterial infections in mice and rats (Nungester, Jourdonais and Wolf [16]). The micro-organisms employed in combination with mucin were as follows: Streptococcus haemolyticus, Staphylococcus aureus, Bacillus coli, Staphylococus albus, Bacillus subtilis, Micrococcus

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ibid. **39**:449-456 (March) 1927; (*f*) Active Immunization Against Experimental Peritonitis, Am. J. Path. **3**:541, 1927; (*g*) Peritonitis: Active Immunization Against Experimental B. Coli Peritonitis, Arch. Int. Med. **41**:42-43 (Jan.) 1928. (*h*) Steinberg, B.: Inflammation of Serous Surfaces: Transfer of Living Leucocytes and Effect on Acute Infectious States, Arch. Path. **25**:785-791 (June) 1938.

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10. Wilen, C. J., and Dragstedt, C. A., cited by Meleney [23c] and by Harvey and Meleney.[23d]

11. Costain, cited by Steinberg.[8a]

12. Lehman, E. P., and Copher, C. H.: Lymphaticostomy: An Experimental and Clinical Study of Thoracic Duct Drainage in General Peritonitis, Arch. Surg. **10**:742-750 (March) 1925.

13. Blalock, A.: Peritonitis: Effects of the Administration of Salt Solution on the Amount of Fluid That Accumulates in the Peritoneal Cavity, Arch. Surg. **26**:1098-1102 (June) 1933.

14. Bergh, G. S.; Bowers, W. F., and Wangensteen, D. H.: Perforation of the Gastrointestinal Tract: Experimental Study of Factors Influencing Development of Peritonitis, Surgery **2**:196-210 (Aug.) 1937.

15. Buchbinder, J. R.; Heilman, F. R., and Foster, G. C.: Experimental Peritonitis: II. The Effect of Hypertonic Dextrose Solution upon Experimental Diffuse Peritonitis, Surg., Gynec. & Obst. **49**:788-793 (Dec.) 1929. Buchbinder, J. R.; Draegemueller, W. A., and Heilman, F. R.: Experimental Peritonitis: Effect of Drainage upon Experimental Diffuse Peritonitis, ibid. **53**:726-729 (Dec.) 1931.

16. Nungester, W. J.; Wolf, A. A., and Jourdonais, L. F.: Effect of Gastric Mucin on Virulence of Bacteria in Intraperitoneal Infections in the Mouse, Proc. Soc. Exper. Biol. & Med. **30**:120-121 (Nov.) 1932. Nungester, W. J.: Results of Inoculation of Poliomyelitis Virus into Mice, ibid. **30**:1128-1129 (May) 1933. Nungester, W. J., and Jourdonais, L. F.: Role of Mucin in the Production of Experimental Pneumonia in Rats, J. Bact. **29**:34 (Jan.) 1935. Nungester, W. J.; Jourdonais, L. F., and Wolf, A. A.: Effect of Mucin on Infections by Bacteria, J. Infect. Dis. **59**:11-21 (July-Aug.) 1936. Nungester, W. J., and Jourdonais, L. F.: Mucin as an Aid in the Experimental Production of Lobar Pneumonia, ibid. **59**:258-265 (Nov.-Dec.) 1936.

catarrhalis, nonmucoid Friedländer bacillus, anthrax bacillus, meningococcus (Rake;[17] Proom;[17a] Cohen[17b]), gonococcus (Miller and Castles[18]), Bacillus typhosus (Henderson, Jamieson and Powell[19]) and pneucomoccus (Nungester and Jourdonais;[16] Gunn and Nungester[20]).

In view of the considerable irregularity of results obtained by most of these methods, the work described was undertaken in order to develop a standardized method for producing experimental peritonitis.

MATERIAL, METHOD AND RESULTS

The strains of micro-organisms employed were as follows:

B. coli (Lewis, S-6, "A" and "R" [from human bowel]; "RF" [from rabbit stool]; "F" "AL" and "O" [obtained during a diarrhea epidemic]; P.M. 677 [taken post mortem from a subject with peritonitis] and many others obtained from subjects with renal sepsis, acute appendicitis and cholangitis); Enterococcus "E" (rabbit stool), and B. typhosus "T.L."

The mucin used was the granular variety (Wilson Laboratory). It was prepared for intraperitoneal injection according to the method of Rake[17c] except that an electric egg beater was employed for a few minutes to break up the mucin suspension instead of the mucin being allowed to soak as in Rake's method. Tragacanth solution was made up according to the procedure of Steinberg.[8]

The strains of B. coli used were grown for eighteen to twenty-four hours on plain agar slants at 37 C. These slants were washed off with saline solution, and the organisms were suspended and diluted in physiologic solution of sodium chloride. Dilution was adjusted so that 1 cc. contained 900,000,000 organisms according to a standard barium sulfate nephelometer.[21] The bacterial suspensions

17. Rake, G.: Method for Titrating Protective Action of Antimeningococcal Serum, Proc. Soc. Exper. Biol. & Med. **32**:1175-1178 (April) 1935; Studies on Meningococcal Infection: Study of an Isolated Epidemic, J. Exper. Med. **61**: 545-548 (April) 1935; Mouse Protection Test in the Standardization of Antimeningococcal Serum, Canad. Pub. Health J. **28**:265-269 (June) 1937.

17a. Proom, H.: The Therapeutic Effect of *p*-Aminobenzenesulphonamide in Meningococcal Infections of Mice, Lancet **1**:16 (Jan. 2) 1937.

17b. Cohen, S. M.: A Study of the Virulence of Meningococcus Strains and the Protective Activity of Antimeningococcus Serum, J. Immunol. **29**:61-62 (April) 1935.

18. Miller, C. P.: Experimental Meningococcus Infections in Mice, Science **78**:340-341, 1933; Study of Experimental Meningococcal Infection: Method, Proc. Soc. Exper. Biol. & Med. **32**:1136-1138 (April) 1935; Study of Experimental Meningococcal Infection: Course of Infection, ibid. **32**:1138-1140 (April) 1935; Study of Experimental Meningococcal Infection: Effect of Anti-Bacterial Immune Sera, ibid. **32**:1140-1142 (April) 1935. Miller, C. P., and Castles, R.: Experimental Meningococcal Infection in the Mouse, J. Infect. Dis. **58**:263-279 (May-June) 1936.

19. Henderson, W.; Jamieson, W. A., and Powell, H. M.: Enhancement of Bacterial Virulence by Gastric Mucin, Proc. Indiana Acad. Sc. **45**:133-138, 1936.

20. Gunn, F. D., and Nungester, W. J.: Pathogenesis and Histopathology of Experimental Pneumonia in Rats, Arch. Path. **21**:813-830 (June) 1936.

21. McFarland, J.: The Nephelometer: An Instrument for Estimating the Number of Bacteria in Suspensions Used for Calculating the Opsonic Index and for Vaccines, J. A. M. A. **49**:1176 (Oct. 5) 1907.

TABLE 1.—*Results of Inoculation with B. Coli Alone and in Combination with Mucin, Tragacanth and "Animal Transfer"*

Animal	Group No.	Strains	Dose	Enhancement	Animal Passage	Total No.	Died		Survived	
							Peritonitis	No Peritonitis	Peritonitis	No Peritonitis
Rabbit	1	Lewis	90,000 to 900,000,000	Mucin in some	0	13	0	4	0	9
Rabbit	2	S6; "F"; "A"; "D"; "AD"; P.M. 677	9,000,000 to 900,000,000	Mucin	0	20	0	3	0	17
Rabbit	3	P.M. 677	9,000,000 to 1,800,000,000	Mucin; tragacanth	+ (repeated)	26	4	5	1	16
Rabbit	4	P.M. 677 (smooth colonies); renal sepsis; acute appendicitis; cholangitis	1,800,000,000	Mucin; tragacanth	+	8	1	2	1	4
Rabbit	5	Rabbit feces (control)	2 to 10 cc. saline suspension	Mucin and none	0	7	6	1	0	0
Rabbit	6	Enterococcus "E"; colon bacillus "RF"	900,000,000 to 1,800,000,000	Mucin	0	12	2	1	0	9
						86	13	16	2	55

were then diluted, and "pour" plates of low dilutions were made for bacterial counts. With this method the error due to dilution was comparatively small (i. e., ± 10 per cent). Organisms suspended in saline solution alone and in saline solution and mucin were injected into the peritoneal cavities of animals with a large bore needle (16 or 18 gage) and syringes of 20 and 50 cc. capacity. Autopsy was performed on all dead animals as soon as possible, usually within one to six hours after death, and cultures were made of the peritoneal fluid and heart's blood in dextrose broth. The surviving animals were killed in a few days to one week after the injection. Intravenous injection of ether or air proved the simplest method of killing the animals. Blood for culture was obtained from rabbits and cats during life by intracardiac puncture. Various tissues were removed for histologic examination. Peritoneal fluid for cytologic and bacteriologic studies was withdrawn by means of peritoneal punctures with an 18 gage needle with a syringe attached. In this manner intestinal trauma was avoided. The experimental animals were of both sexes and miscellaneous breeds except as otherwise indicated. They were in a good state of nutrition and were quarantined prior to the experimental work.

As may be seen from the results recorded in table 1, a total of 86 rabbits was employed in attempts to produce experimental peritonitis. A variety of strains of B. coli and enterococcus, alone and in combination with mucin and tragacanth, were injected into the peritoneal cavity. The virulence of some strains was enhanced by passage through animals prior to the experiments. Moreover, some animals received rabbit feces intraperitoneally. After the treatment described, 29 rabbits died, and 57 survived for from three to seven days before they were killed. Seven of the rabbits that died (and most of those which received rabbit feces) showed evidence of peritonitis. There was a small amount (10 to 30 cc.) of serosanguineous fluid in the peritoneal cavities of these animals. The intestines were not dilated, and there was no evidence of any purulent exudate. In some instances the vessels of the mesentery were engorged. No lymphadenopathy was observed. One animal had a volvulus of the intestine, which may have contributed to the peritonitis. Still another had pneumonia involving several lobes in addition to the peritonitis. Three of these 7 animals showed scattered areas or only a single area of localized fibrinous peritonitis. The attempts failed to elicit regularly an easily reproducible purulent peritonitis under standard conditions in rabbits.

However, the strains of B. coli which had passed through mice (4 times) and rabbits (10 times) when injected with mucin into rats produced peritonitis.

It is noteworthy (table 1, group 6) that the minimal lethal peritonitis-producing dose was 5,000 times less with mucin than with saline solution (90,000 and 450,000,000 organisms respectively).

In view of the encouraging results with rats, a series of experiments applying the aforementioned method was carried out in cats, as follows:

Ether given by inhalation or pentobarbital sodium given intravenously was employed at the onset in preparation for cardiac and peritoneal punctures and aspirations. Later, however, these procedures were performed in unanesthetized cats. After some preliminary work with various strains of B. coli (table 3, groups 1 and 2) a good peritonitis-producing strain was isolated. Moreover, the virulence of the strain was increased by passage through cats (table 3, groups 3-8). Mucin and tragacanth were both employed as enhancing agents. With the former, doses of B. coli as low as 45,000,000 were capable of causing a fatal peritonitis, whereas with the latter 2,700,000,000 organisms were required. Sixty-three

TABLE 2.—*Inoculation of Mice and Rats with B. Coli and B. Typhosus Enhanced by Mucin*

Animal	Group	Strain	Dose	Enhancement	Animal Passage	Total No.	Died		Survived	
							Peritonitis	No Peritonitis	Peritonitis	No Peritonitis
Swiss mouse	1	"F"; "AD"; "D"	90 to 90,000	Mucin	0	10	0	1	0	9
Swiss mouse	2	Typhoid TL	Loopful	Mucin in 1	0	2	1	0	0	1
Swiss mouse	3	P.M. 677	9,000	Mucin in 1	0	2	1	0	0	1
Swiss mouse	4	P.M. 677	9 to 9,000	Mucin (except one)	+	5	3	0	1	1
Swiss mouse	5	P.M. 677	9 to 900	Mucin in some	+	9	3	1	1	4
Rat	6	P.M. 677	90,000 to 900,000,000	Mucin	+	24	16	3	1	4
						—	—	—	—	—
				Totals for mice		28	8	2	2	16

TABLE 3.—*Inoculation of Cats with Various Strains of B. Coli, in Saline, Mucin and Tragacanth*

Group	Strain	Dose	Enhancement	Animal Passage	Total No.	Results		Survived		Cultures		
						Died of Peritonitis	No Peritonitis	Peritonitis	No Peritonitis	Blood Culture	Heart	Peritoneum
1	P.M. 677	1,800,000,000	Mucin	+	4	1	..	..	3	....	1+	1+
2	P.M. 677; P.M. "R"	3,000,000,000 to 4,500,000,000	Mucin (4) and tragacanth	±	8	1	2	..	5	....	3+	3+
3	"R"	4,000,000,000 to 4,500,000,000	Mucin	+	8	6	1	..	1	....	6+	6+
4	"R"	4,000,000,000 to 4,500,000,000	Tragacanth or saline	+	9	2	1	..	6	....	3+ 1 negative	2+ 3 negative
5	"R"	9,000,000 to 4,500,000,000	Mucin	+	35	31	..	..	4	16+ 1 negative	11+ 1 negative	31+ 1 negative
6	"R"	900,000,000 to 5,400,000,000	Tragacanth	+	13	11	1	..	1	5+ 1 negative	4+ 1 negative	6+ 2 negative
7	"R"	7,200,000,000 to 9,000,000,000	Saline	+	3	2	1	..	..	1+ 1 negative	....	2+ 1 negative
8	"R"	9,000,000 to 63,000,000	Mucin	+	49	45	..	..	4	+ in those died	+ in dead	+ in dead

million organisms in 10 cc. of mucin regularly produced fatal purulent peritonitis (table 4, group 3). Thus, the minimum lethal peritonitis-producing dose was 42 times greater with gum tragacanth than with mucin and regularly produced with the latter (table 4, groups 1-3).

Blood cultures were made in a great majority of cases, and these were found to yield B. coli as early as one and one-half hours after intraperitoneal injection of the B. coli–mucin mixture. In the cases of the animals which succumbed the blood cultures usually yielded bacteria four and eight hours after the injections. The greater the dose of organisms injected intraperitoneally, the more overwhelming was the bacteremia. With very large doses (4,500,000,000) innumerable organisms were recovered in the blood, whereas with doses from 90,000,000 to 1,800,000,000 the colony count was 10 to 100 per cubic centimeter of blood.

Peritoneal aspiration (after injection of organisms) demonstrated a variety of white cells, mainly polymorphonuclear leukocytes but including mononuclears, lymphocytes and mesothelial cells. Organisms were found free and also within phagocytic cells. In cases in which the peritonitis terminated fatally the number of organisms was very large, whereas in the surviving animals it was minimal (5 to 10 per oil immersion field).

TABLE 4.—*Summary of Experiments on Cats with Mucin and with Tragacanth as Enhancing Agent*

Group	Strain	Dose	Inoculum	Total No.	Died Peritonitis	Percentage
1	(Rafal) human B. coli	9,000,000 to 4,500,000,000	Mucin	100	85	85
2	(Rafal) human B. coli	900,000,000 to 5,400,000,000	Gum tragacanth	20	14	70
3	(Rafal) human B. coli	63,000,000	Mucin	41	41	100

Necropsy in cases of death from peritonitis showed diffuse purulent peritonitis with dark yellow and yellow-green thick pus varying in amounts from 30 to 100 cc. The blood vessels of the parietal and visceral peritoneum were engorged. Both large and small intestinal loops were distended and rigid. The mesenteric nodes were often enlarged and succulent. Fibrinous exudate with a dull red luster was frequently observed on the visceral and parietal layers of the peritoneum. Histologic sections verified the gross appearance. An acute inflammatory exudate (mainly polymorphonuclear leukocytes) was present throughout the serosa of the intestinal wall and usually reached down to the muscularis.

COMMENT

In 1925, Steinberg,[8] following the work of Benians,[7] described a method of producing experimental peritonitis in dogs with a broth suspension of an agar culture of B. coli mixed with tragacanth. The dose injected was 40 cc. containing 8,000,000,000 bacterial cells. Trusler and Moss [22] elicited peritonitis in rabbits by means of gum tragacanth and B. coli. The peritonitis observed on postmortem examination was

22. Trusler, H. M., and Moss, J. M.: The Treatment of Colon Bacillus Peritonitis in Rabbits with Escherichia Coli Anti-Serum, Surg., Gynec. & Obst. **69**:34-36 (Jan.) 1939.

of a serosanguineous type. This was accompanied by septicemia. The animals were successfully protected by an antitoxic anti-colon-bacillus serum (i. e., containing Shwartzman antibodies [Lilly]).

It may be emphasized here that in the experiments of Trusler and Moss the rabbits never showed evidence of peritonitis similar to that seen in the human being. The experiments reported in this paper demonstrated serosanguineous peritonitis in rabbits resembling the condition described by Trusler and Moss except that mucin instead of tragacanth was used as the enhancing agent.

In contrast, however, when B. coli and mucin was given intraperitoneally to cats the minimal lethal dose necessary for the production of peritonitis was considerably smaller than in Steinberg's experiments. Thus, a dose of 63,000,000 organisms produced fatal lesions, whereas Steinberg required as many as 8,000,000,000 per dog. Moreover, it is of interest that 63,000,000, the dose indicated, or a greater dose, produced the results recorded with absolute uniformity. The pathologic process followed closely the human type, being consistently diffuse and purulent. It differed, however, in that an invasion of the blood stream accompanied the local condition. It is hoped that peritonitis elicited under standard conditions [23] may be of value in further studies on etiology and treatment. Work in this direction is under progress and will be reported later.

SUMMARY

The injection of a human strain of B. coli suspended in mucin invariably produced fatal suppurative bacterial peritonitis in cats. The method employed was simple and lent itself to standardization. The minimal dose for the production of lethal peritonitis was 63,000,000 organisms. An identical method and technic were effective in the production of peritonitis in rats and mice but not in rabbits.

23. (*a*) Behrendt, R. A.: Experimental Peritonitis Produced by the Injection of Bacteria, Proc. Soc. Exper. Biol. & Med. **31**:543-544 (Feb.) 1934. (*b*) Hinmann, F.: Experimental Study of Uretero-Intestinal Implantation: Cause of Peritonitis, Surg., Gynec. & Obst. **62**:909-917 (June) 1936. (*c*) Meleney, F. L.: Peritonitis, in Nelson Loose-Leaf Living Surgery, Survey of Literature, Service Volume, New York, Thomas Nelson & Sons, 1932, p. 42. (*d*) Harvey, H. D., and Meleney, F. L.: Peritonitis: Collective Review of Significant Literature for Six and One-Half Years, Internat. Abstr. Surg. **67**:339-355 (Oct.) 1938.

TUMOR OF THE THALAMUS

A VENTRICULOGRAPHIC ENTITY

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In surgery of the brain the policy has been evolved of pronouncing final judgment as to the operability and prognosis of a tumor only after exploration and microscopic examination. In few instances will the experienced surgeon feel prepared to predict with finality even the pathologic type of the tumor, not to mention its operability. Although a properly made ventriculogram will localize a tumor to a satisfactory degree, it usually cannot be relied on to show the type of tumor. In any instance in which the ventriculogram can be relied on to indicate an inoperable tumor, it provides valuable information to the surgeon.

Tumors arising in the thalamus are unique in this respect. The ventriculographic picture is unmistakable, and the tumor, because of its position if not because of its cell type, is clearly inoperable. Four cases are presented here to illustrate the cardinal ventriculographic features of tumor of the thalamus. Another case has been presented by McConnell and Childe.[1]

In 3 of the cases reported here the diagnosis was proved by autopsy or by operation. In the fourth case there were clinical findings which together with the ventriculogram made the diagnosis sufficiently clear. The first case, that of J. P., was reported in a previous paper [2] but is incorporated here for additional emphasis.

REPORT OF CASES

CASE 1.—J. P., a Negro aged 38, was referred to us by Dr. E. W. Anderson, of Des Moines, Iowa, in January 1936.

Three months previously he had noticed severe pain in the back of the head and neck. After this he had vomited many times. He had become irrational and disoriented two weeks before admission to the hospital.

From the Departments of Surgery and Neurology, the neurosurgical service, College of Medicine, State University of Iowa.

1. McConnell, L. H., and Childe, A. E.: Tumors Involving the Basal Ganglia, Lateral Ventricles, Brain Stem and Cerebellum, Arch. Neurol. & Psychiat. **37**: 56-67 (Jan.) 1937.

2. Hyndman, O. R.: Cerebral Pneumography: Ventriculographic Interpretation of Tumors In and About Third Ventricle, Aqueduct of Sylvius and Fourth Ventricle, Arch. Surg. **36**:245-291 (Feb.) 1938.

Examination.—There were general tenderness to percussion of the skull, bilateral paresis of the sixth nerve, advanced bilateral papilledema and dehydration. The patient swayed when his heels were together and his eyes closed. There were continued choreoathetoid movements of the upper extremities; these were at first interpreted as cerebellar ataxia, but the patient performed the usual cerebellar tests well. There were complete astereognosis on the right side and loss of sensation to light touch. The patient frequently tried to wipe some fantom object from the right palm. There was overreaction to the light scratch of a pin

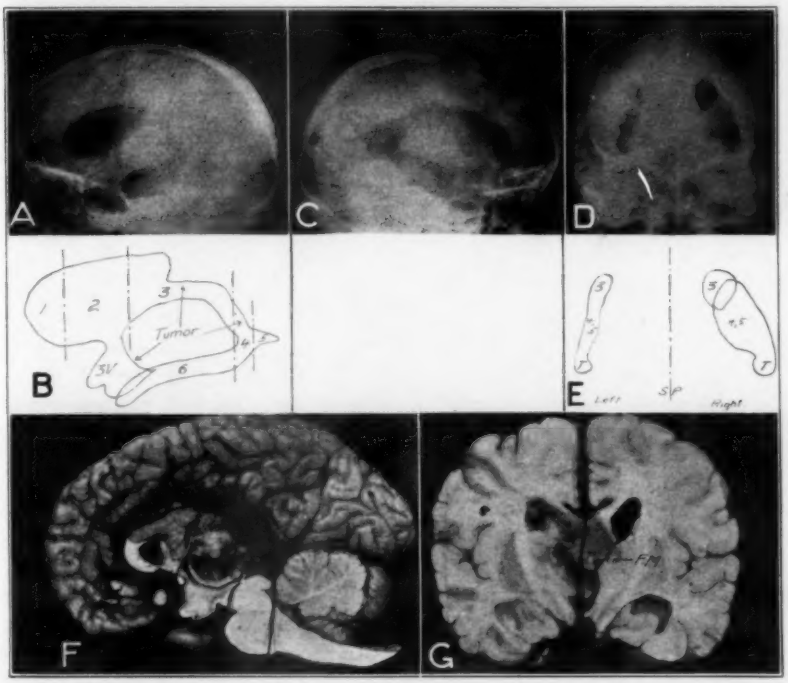

Fig. 1.—*A*, lateral view, right side down, showing a filling defect in parts 3 and 4 and in the posterior two thirds of the third ventricle. (Division of the lateral ventricle into parts 1 to 6 is in conformity with the scheme proposed by Torkildsen, A., and Penfield, W.: Ventriculographic Interpretation, Arch. Neurol. & Psychiat. **30**:1011-1021 [Nov.] 1933. The scheme is roughly indicated in *B*.) *B*, diagrammatic representation of *A*. *3V* indicates the third ventricle. *C*, lateral view, left side down, showing the right ventricle. In a previous report [2] it was recorded that a filling defect existed in both lateral ventricles. Further study has corrected this interpretation. We feel that the point is important, because in none of these 4 cases was there a major filling defect in the contralateral ventricle. *D*, posteroanterior view (occiput up), illustrating the filling defect in parts 3 and 4. *E*, diagrammatic representation of *D*. *T* indicates the temporal horns (part 6); *SP*, the midsagittal plane. *F*, photograph of the brain, illustrating how the tumor obliterates the posterior aspect of the third ventricle as well as the massa intermedia. The wire is through the aqueduct of Sylvius. *G*, photograph of the brain, illustrating how in this case the tumor has actually invaded part 3 of the ipsilateral ventricle. *FM* indicates the free margin of the tumor.

on the right arm, but this was not present on the left arm. The mental reaction was noteworthy. When spoken to or engaged in conversation the patient would often give rational answers, but as soon as he was left to himself he would mutter irrationally and call for his sister and mother.

There were advanced papilledema on both sides, generalized areflexia and a spinal fluid pressure of 590 mm. of water with the patient in the prone position. Ventriculograms are shown in figure 1.

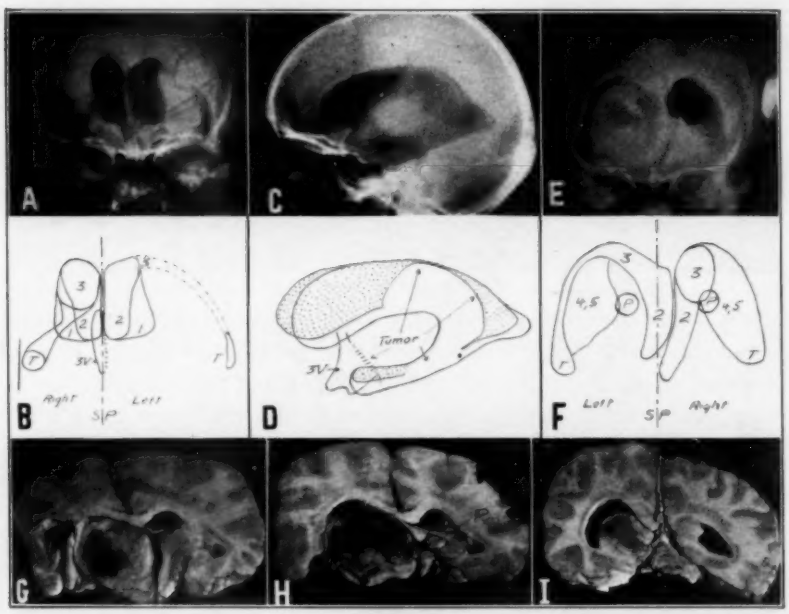

Fig. 2.—*A*, anteroposterior view (brow up), illustrating the following points: 1. After a complete filling of the ventricles with air the anteroposterior view is itself characteristic. 2. Air has found easy egress through the foramens of Monro to the opposite ventricle. (This was true in all cases.) 3. In spite of the size of the tumor the contralateral ventricle is normal in position and contour (except for uniform dilatation). 4. On the side on which the tumor is present there is a filling defect in the third ventricle; parts 1 and 2 show no filling defect, while parts 3 and 4 are markedly flattened upward and laterally and in this case part 6 is shifted laterally. *B*, diagrammatic representation of *A*. *T* indicates the temporal horns (part 6). *C*, lateral view, right side down, illustrating the sharply outlined filling defect in part 3 and most of part 4 of the left lateral ventricle and obliteration of the posterior aspect of the third ventricle. *D*, diagrammatic representation of *C*. The left lateral ventricle is stippled. *E*, posteroanterior view (occiput up), illustrating how part 3 and most of part 4 are flattened upward and laterally. It is striking that part 5 (posterior horn) is shifted only a little from its normal position. *F*, diagrammatic representation of *E*. *P* indicates perforator openings; *T*, the temporal horns (part 6). *G*. *H* and *I*, photographs of the brain, the sections being made anterior to part 4, through part 4 and behind part 4 respectively. They illustrate how the tumor encroaches on the third ventricle and flattens parts 3 and 4 of the ipsilateral lateral ventricle without encroaching on the contralateral ventricle. Figure 1 explains the presence of a shadow representing parts 4 and 5 in *E* and *F*. *P* indicates the pulvinar of the contralateral thalamus.

Operation.—This was our first case of this kind, and exploration was done, material for biopsy being obtained through the corpus callosum. The tumor proved to be a glioblastoma. The patient died in the hospital, and postmortem examination revealed a tumor of the thalamus (fig. 1 *F* and *G*).

CASE 2.—H. Z., a white woman aged 42, was referred to us by Dr. D. H. Nord, of Cambridge, Iowa, on Aug. 24, 1937.

Her illness had begun in the spring, with loss of vigor, numbness of the right side, awkwardness of the right leg and frontal headache.

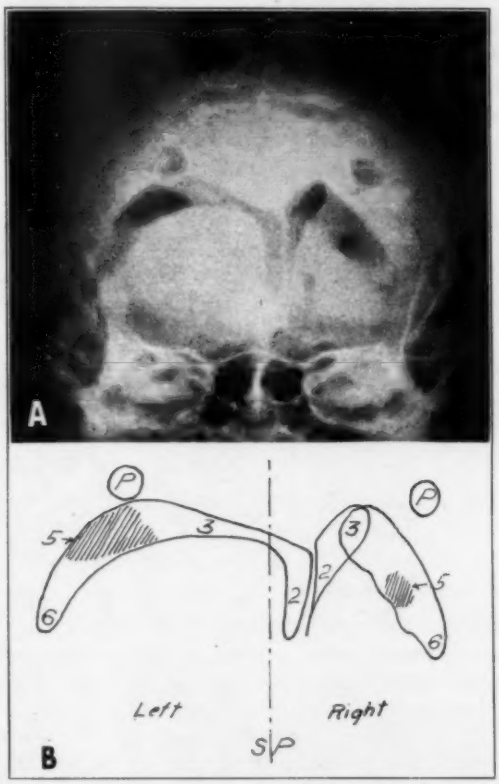

Fig. 3.—*A*, posteroanterior view (occiput up), illustrating the upward and lateral flattening of part 3 on the left and in this case a lateral shift of parts 4, 5 and 6. *B*, diagrammatic representation of *A*. *P* indicates perforator openings; *SP*, the midsagittal plane.

Examination.—By August the patient was mentally confused and presented right hemiplegia, hemianesthesia and hemianopia. The right pupil did not react to light. Although the optic disks appeared normal on admission, mild papilledema developed during hospitalization. The spinal fluid pressure with the patient in the prone position was 130 mm. of water. Ventriculograms are shown in figure 2. A diagnosis of tumor of the thalamus was made. Operation was not thought justified.

The patient died in the hospital. The postmortem observations are shown in figure 2, *G*, *H* and *I*.

Case 3.—R. S., a white man aged 47, was referred to us by Dr. L. A. Miller, of North English, Iowa, on Nov. 6, 1937.

Eight months previously his illness had begun, with "hot flashes" in the left arm and leg. These had been followed by "dizzy spells" lasting about five minutes. He had been nervous and drowsy and had complained of roaring in the left ear for two months.

Examination.—There were a fine vertical nystagmus and right homonymous hemianopia. The spinal fluid pressure was 360 mm. of water with the patient in the prone position. Examination otherwise gave essentially negative results.

A ventriculogram is shown in figure 3.

Operation.—Through a small craniotomy opening an incision was made in the brain, the left posterior horn being exposed. It was then obvious that an expanding mass existed in the thalamus. A small biopsy specimen was obtained from the tumor, which proved to be a glioblastoma.

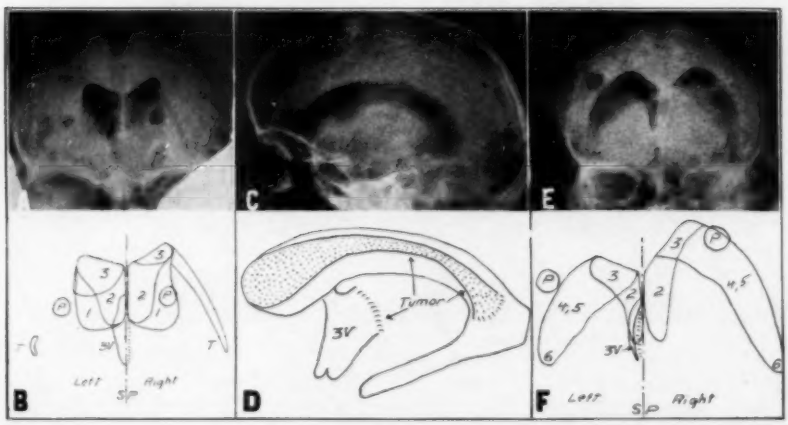

Fig. 4.—*A*, anteroposterior view, showing a filling defect in the right half of the third ventricle and part 3 flattened upward on the right. Except for dilatation the left lateral ventricle is normal in position and contour. *B*, diagrammatic representation of *A*. *P* indicates perforator openings. *C*, lateral view, left side down, showing obliteration of the posterior aspect of the third ventricle and flattening of part 3. *D*, diagrammatic representation of *C*. *E*, posteroanterior view, showing a filling defect in the right half of the third ventricle and flattening of part 3. *F*, diagrammatic representation of *E*.

Course.—The patient improved somewhat after a decompression and died three months later at home, after being restless and completely demented for two weeks.

Case 4.—L. K., a white man aged 32, was referred to us by Dr. John Marker, of Davenport, Iowa, in June 1938.

His illness had begun four months previously, with weakness and numbness of the left foot. This progressed to involve the entire left side, so that at the time of admission the left side was hemiplegic and numb. He did not complain of headache.

Examination.—There were total left hemiplegia and total left hemianesthesia. There was left homonymous hemianopia. There was no papilledema, and the spinal fluid pressure with the patient in the prone position was 85 mm. of water. The mental status seemed unimpaired.

Ventriculograms are shown in figure 4, and a diagnosis of inoperable tumor of the right thalamus was made.

The patient died at home two months later, after a two day period of coma. Permission for postmortem examination was refused.

SUMMARY

Four cases of tumor of the thalamus are presented, with ventriculograms. The tumor was on the left side in 3 cases and on the right in 1. The tumors in the 3 cases in which the diagnosis was proved were glioblastomas. The time from the onset of symptoms until the diagnosis was made was three, five, eight and four months respectively. In each case the tumor was well advanced at the time the patient was seen in the hospital. The 4 patients died four, six, eleven and six months respectively after the onset of symptoms. The death of the first patient (J. P.) was no doubt hastened by the operation.

While one would certainly suspect a tumor of the thalamus from the clinical findings in all but case 3, the ventriculograms leave no doubt concerning the diagnosis.

It is of interest that in 2 cases the spinal fluid pressure was within normal limits and that in 3 cases, including these 2, papilledema was not present or developed late.

The ventriculographic pictures were all consistent and unmistakable, the two cardinal features being (1) flattening of part 3 upward and to the ipsilateral side, which can be seen in the anteroposterior view but more definitely in the posteroanterior view, and (2) obliteration of the posterior aspect of the third ventricle and the "negative" shadow of the massa intermedia.

Other features are the absence of filling defect in the contralateral ventricle, and the fact that little if any shift occurs in its position and the fact that parts 1 and 2 on the involved side remain intact and the foramens of Monro unobstructed. In some cases, depending on the size of the tumor, parts 4, 5 and 6 will be shifted to the ipsilateral side.

CONCLUSION

The ventriculographic findings in the case of tumor of the thalamus are consistent and unmistakable and indicate an inoperable tumor. (The cardinal signs are given in the summary.)

SCOLIOSIS FOLLOWING EMPYEMA

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A survey was made of the records of all the patients with nontuberculous empyema treated by operation in this institution during the years 1932 to 1936 inclusive. This study was undertaken because of the impression that scoliosis was an occasional sequel to operation for empyema. It was felt that careful observation of all the factors involved might explain why in some patients empyema was followed by persistent scoliosis while others, with apparently similar involvement, recovered without any permanent spinal deformity.

The observation has been made by Chandler [1] that in almost all cases of acute empyema scoliosis develops with the concavity toward the diseased side. This type of scoliosis is slight (18 degrees maximum) and in almost all cases subsides when the empyema is healed. Bisgard,[2] Cleveland,[3] Gaugele,[4] Gurd,[5] Hedblom,[6] Kleinberg,[7] Rey,[8] Steindler [9] and von Beust [10] studied the problem of scoliosis in various types of

From the Surgical and Orthopedic Services of the Mount Sinai Hospital.

1. Chandler, E. A., in discussion on Cleveland, M.: Lateral Curvature of the Spine Following Thoracoplasty in Children, J. Thoracic Surg. **6**:595, 1937.

2. Bisgard, J. D.: Thoracogenic Scoliosis: Influence of Thoracic Disease and Thoracic Operations on the Spine, Arch. Surg. **29**:417 (Sept.) 1934; Skeletal Deformities in Children Resulting from Empyema and Methods of Prevention, J. Thoracic Surg. **6**:609, 1937; Acute Empyema: The Use of a Bradford Frame to Promote Dependent Drainage and to Prevent Scoliosis, ibid. **6**:624, 1937; Experimental Thoracogenic Scoliosis, ibid. **4**:435, 1935.

3. Cleveland, M.: Lateral Curvature of Spine Following Thoracoplasty in Children, J. Thoracic Surg. **6**:595, 1937.

4. Gaugele, K.: Die postpleuritische Skoliose und ihre Verhütung, München. med. Wchnschr. **66**:442, 1919.

5. Gurd, F. B.: Scoliosis Accompanying Chronic Infected Open Pneumothorax, Arch. Surg. **5**:366 (Sept.) 1922.

6. Hedblom, C. A.: Deformity of the Thorax Secondary to Pleural or Pulmonary Disease, J. A. M. A. **94**:162 (Jan. 18) 1930.

7. Kleinberg, S.: Scoliosis, New York, Paul B. Hoeber, Inc., 1936.

8. Rey, J.: Die Bedeutung der postpleuritischen Skoliose im Kindesalter, München. med. Wchnschr. **70**:176, 1923.

9. Steindler, A.: Diseases and Deformities of the Spine and Thorax, St. Louis, C. V. Mosby Company, 1929.

10. von Beust, A. T.: Ueber den Einfluss der Rippenresektion auf die Form der Wirbelsäule (Beitrag zu der Arbeit Hoesslys: "Gibt es eine operative Behandlung der Skoliose?"), Deutsche Ztschr. f. Chir. **158**:154, 1920.

pulmonary disease. There are two main types of scoliosis resulting from intrathoracic disease:

1. Scoliosis following empyema. The concavity is toward the empyema, and there is little or no rotation of the vertebral bodies.

2. Scoliosis complicating thoracoplasty. The convexity is toward the resected ribs.

There are exceptions to the rule, however, and the early curve may be convex on the side of the empyema if there is an extremely massive effusion. The curve resulting from thoracoplasty almost always has its convexity on the surgically treated side but may be influenced by the preexisting opposite curve caused by the empyema. Occasionally the two curves neutralize each other, and scoliosis following empyema with the concavity on the diseased side disappears after thoracoplasty.

This report is based on a study of all the patients with nontuberculous empyema treated by operation in the surgical services of the Mount Sinai Hospital from 1932 to 1936 inclusive who returned for examination of the spine. There was an opportunity to examine the spinal columns of 65 patients at the end of periods varying from one to six years after operation for empyema. These unselected patients represent one third of all those operated on and presumably comprise a representative sample.

Of the 65 patients, 5 had clinical evidence of scoliosis, but the curve was severe in only 2. By a severe curve is meant a deforming, obvious curve that cannot be hidden by clothing. Curves of 20 degrees or less may be considered slight and curves of 35 degrees or more, severe. In the 2 patients with severe curvature the primary curves were, respectively, 97 degrees and 44 degrees.[11]

The case histories of the 2 patients with severe curvature follow. The curvatures were of contrasting types; the first had its convexity on the side of an extensive rib resection ("thoracoplasty scoliosis"); the second was concave on the side of the empyema, a typical post-empyemic curve.

REPORT OF CASES

CASE 1.—M. R., a boy aged 11 years at the time of admission (1930) entered the hospital because of cough and dyspnea of three weeks' duration. Physical signs and roentgen examination revealed a pleural effusion on the right side, pushing the heart and mediastinum to the left. It was noted on the roentgenogram that there was no spinal curvature at the time (fig. 1*A*). A stab thoracotomy and underwater drainage through the eighth intercostal space posteriorly were performed on the day of admission. A week later 1 inch (2.5 cm.) of the eighth rib was excised posteriorly, and a large empyema cavity was drained of pus

11. Ferguson, A. B.: Study and Treatment of Scoliosis, South. M. J. **23**:116, 1930.

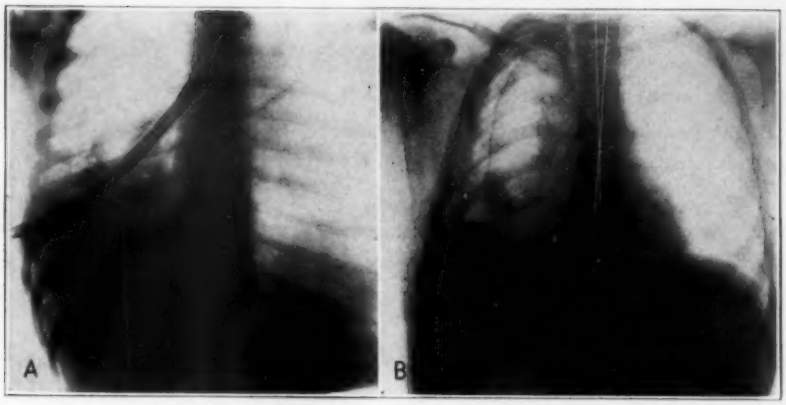

Fig. 1 (case 1).—*A*, roentgenogram taken on admission of the patient to the hospital, three weeks after the onset of illness. At this time there was no evidence of a spinal curvature. *B*, roentgenogram taken nine months after onset of the illness. At that time a slight spinal curvature (5 degrees) was noted concave to the side of the empyema.

Fig. 2 (case 1).—Appearance of the patient eight years after onset of the illness.

containing Pneumococcus type I. One month later a portion of the ninth rib was excised posteriorly, and the lung was found markedly collapsed. The boy was readmitted eight months after the original operation, with chronic empyema. Roentgen examination on readmission revealed a slight (5 degree) curve, concave on the side of the empyema (fig. 1 *B*). A partial thoracoplasty consisting of resection of four ribs with intercostal tissues and pleura was performed in an attempt to obliterate a large intrapleural space. Nine months after the thoracoplasty, marked thoracic scoliosis, convex to the right, was noted. There was a compensatory lumbar curve to the left, the right shoulder was elevated and the right scapula prominent. Roentgen examination at this time revealed that the fifth to the tenth ribs inclusive had been resected. Soon after this, an unsuccessful attempt to correct the scoliosis by means of Risser (hinged) jackets was made in another institution. Three and three-quarters years after the thoracoplasty the patient was readmitted to this hospital because of fever and pain in the right side of the chest. His wound had reopened spontaneously. Bony bridges together with the portions of two ribs above them were excised, and two months later further rib resections were performed. Seven months after the last procedure the wound was healed. Six and one quarter years after the original operation the scar adherent to the pleura broke down, and at this time a plastic operation on the soft tissues was successful in closing the wound. In December 1937 clinical (fig. 2) and roentgen (fig. 3 *A*) examinations revealed a dorsal curve to the right of 97 degrees, with the apex at the tenth dorsal vertebra. There were dorsal kyphosis and an acute lumbosacral angle. The ribs on the right side were oblique, and those on the left side, horizontal. There was marked rotation of the vertebral bodies.

The exercise tolerance test showed moderate dyspnea and slight fatigue. The venous pressure was 6 cm., the vital capacity [12] 1,200 cc. and the circulation time thirteen seconds, the results of all the tests except that for vital capacity being within normal limits. The scoliosis was so extreme that it caused dysphagia due to displacement of the esophagus, as demonstrated by roentgen studies after ingestion of a barium sulfate meal (fig. 3 *B*).

Summary of Case 1.—The patient had a slight postempyemic curve (5 degrees) with the concavity on the diseased side. Nine months after a thoracoplasty this had been transformed into marked scoliosis in the opposite direction, convex on the side of operation. In the next six years the curvature progressed to 97 degrees.

Case 2.—S. L., a girl aged 14 years, was admitted to the hospital in 1936 with the following history:

At the age of 2½ years there was empyema on the right, the pus containing Staphylococcus aureus. This was drained through an intercostal incision. Four years later, when the patient was 6 years old, the mother noticed a spinal curvature, which has been treated by braces and plaster casts ever since. Six months before admission to the Mount Sinai Hospital the patient had been admitted to another institution, where drainage had been done for a recurrence of the empyema. Since that time the wound had remained open. There was marked scoliosis in the upper dorsal part of the spine, visible on both clinical and roentgen examination, with the concavity on the side of the empyema. There was a draining sinus in the seventh space and dulness on percussion of the entire right side of the

12. Flagstad, A. E., and Kollman, S.: Vital Capacity and Muscle Study in One Hundred Cases of Scoliosis, J. Bone & Joint Surg. **10**:724, 1928.

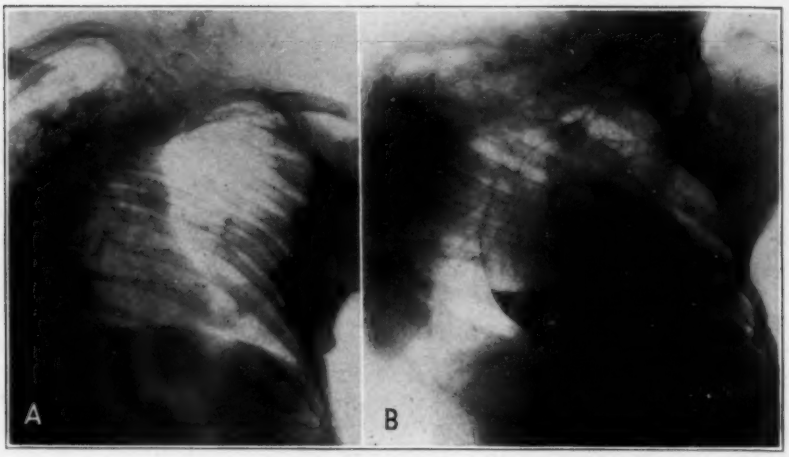

Fig. 3 (case 1).—*A*, severe spinal curvature (97 degrees) with convexity to the side of the thoracoplasty. *B*, displacement of the esophagus, demonstrated by roentgen studies after ingestion of a barium sulfate meal. The condition produced dysphagia.

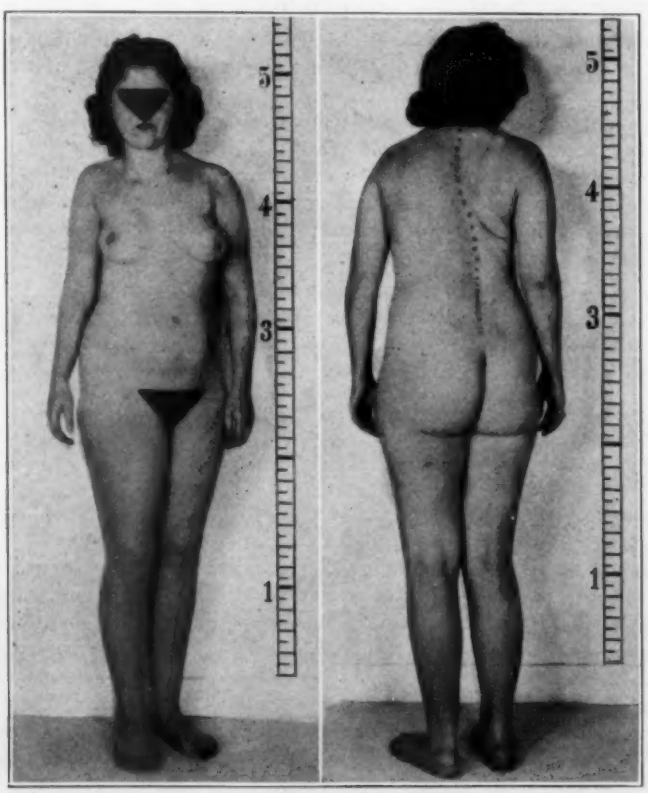

Fig. 4 (case 2).—Appearance of the patient fifteen years after onset of the illness.

chest. Roentgen examination showed that there had been a resection of the seventh, eighth and ninth ribs on the right side in the posterior axillary line, with bony bridging. Operation consisted of excision of a fused mass of bone at the old operative site together with thickened pleura and revealed extensive chronic empyema, with a collapsed lung. The wound healed nine months after the operation, and a plaster jacket and later a brace were applied in an attempt to correct the spinal curvature. In January 1938 clinical (fig. 4) and roentgen (fig. 5) examination revealed thoracic scoliosis without rotation of the bodies, with the apex at the sixth dorsal vertebra. The curve was severe (44 degrees) and had its concavity on the right, the side of the empyema.

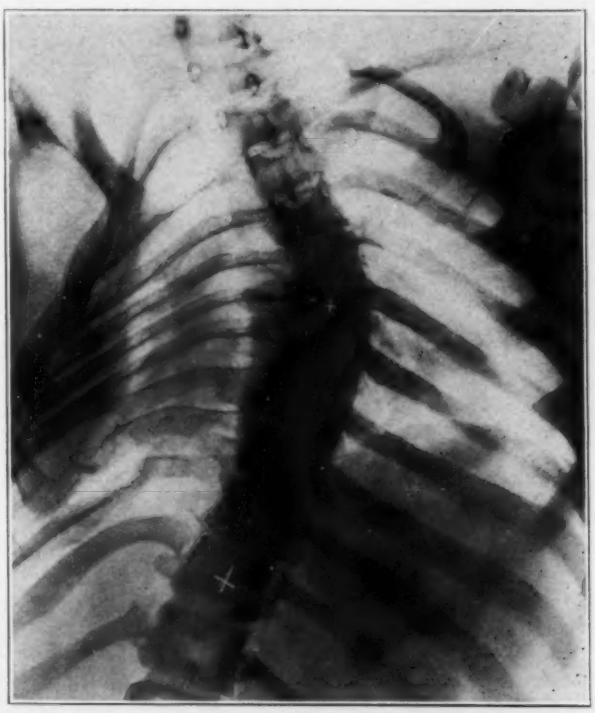

Fig. 5 (case 2).—Severe spinal curvature (44 degrees) concave to the side of the empyema.

Summary of Case 2.—The child was operated on at the age of 2½ years for empyema on the right side, which was followed by scoliosis concave to the diseased side. Four years later this was severe enough to attract the mother's attention. Although treated by braces and jackets, it progressed to 44 degrees. This was the only severe empyemic curve in our series.

Three patients presented slight curves. Two were patients with chronic empyema beginning at the age of 12, on whom multiple short rib resections had been performed. When observed eighteen years later, both had high dorsal curves, of 17 degrees and 12 degrees,

respectively, with the concavity on the side of the empyema and compensatory dorsolumbar curves in the opposite direction.

The remaining patient, a boy, had chronic empyema beginning at the age of 4 years. A partial thoracoplasty was done at the age of 10 years. When observed four years later, he had a curve of 9 degrees with the convexity on the diseased side.

An analysis will now be made of the 60 cases in which empyema was not followed by lasting scoliosis. For purposes of analysis the cases

Fig. 6.—Patient showing no spinal curvature in spite of an extensive thoracoplasty for chronic empyema.

are divided into groups according to the age of onset, and the patients in each age group are subdivided into those with acute and those with chronic empyema.

Four of the patients were infants under 1 year of age. Of these, 3 had acute empyema; in 2 a stab thoracotomy and in the other a small rib resection was done before healing occurred.

The fourth patient was of unusual interest because chronic empyema beginning in infancy and requiring extensive surgical treatment, includ-

ing a Keller[13] thoracoplasty at the age of 8 years, was not followed by scoliosis. When the child was observed three years later there was no evidence of a spinal curve (fig. 6).

In 24 patients the condition began between the ages of 1 and 5 years inclusive. In 22 it was acute and healed rapidly, but in 2 it was chronic. In neither of these 2 did scoliosis develop, in spite of multiple operations for chronic empyema.

In 12 patients the empyema began between the ages of 6 and 10 years. In 11 of these it was acute and was rapidly cured by surgical treatment; in the twelfth it became chronic. This patient, in spite of extensive surgical treatment for chronic empyema, did not have scoliosis.

In the age group from 11 to 20 years there were 2 patients with acute empyema and 1 in whom the empyema became chronic. In spite of extensive surgical procedures for chronic empyema beginning at the age of 17 (the patient was a girl) no scoliosis occurred.

In the group of patients 21 years of age or older, there were 14 with acute and 4 with chronic empyema. In none of these was the empyema followed by scoliosis. We do not believe that an analysis of the observations on each patient is warranted, because the disease began after growth had ceased.

SUMMARY

This paper is based on a study of 65 patients with pyogenic nontuberculous empyema who were operated on in the years of 1932 to 1936 inclusive in the surgical services of the Mount Sinai Hospital. This group includes all patients who returned in 1938 for examination of the spine.

Five patients showed clinical evidence of scoliosis, which was marked in 2. The most severe curve, 97 degrees, followed a thoracoplasty at the age of 12 years for chronic empyema. The scoliosis was of the usual thoracoplasty pattern, with the convexity on the side of operation and with considerable rotation of the vertebral bodies. Treatment with various types of jackets was of no avail. The other severe scoliosis followed chronic empyema for which operation was first performed when the patient was 2 years of age. The curvature was noted four years later and progressed in spite of treatment with jackets and braces. The scoliosis was marked (44 degrees) at the time of admission, when the patient was 14 years of age. It was of the postempyemic type, with the concavity toward the diseased side and without rotation of the vertebral bodies. In the remaining 3 patients the curvature was slight, varying from 5 to 17 degrees. In 2 of these the scoliosis followed

13. Keller, W. L.: The Treatment of Chronic Empyema, Ann. Surg. **76**: 549, 1922.

chronic empyema for which operation was performed when the patients were 12 years of age, the curvatures being of the postempyemic type previously described. A third patient had a thoracoplasty type of curvature after thoracoplasty for chronic empyema at the age of 10 years.

Sixty patients showed no evidence of scoliosis. The accompanying table gives the age at onset and the type of empyema in their cases.

Age at Onset and Type of Empyema in Patients Without Scoliosis

Age, Years	Number of Cases	Acute Empyema	Chronic Empyema
Under 1	4	3	1
1 to 5	24	22	2
6 to 10	12	11	1
11 to 20	2	2	0
Over 20	18	14	4

None of the 52 patients with acute empyema whose wounds healed permanently in the mean time of four months or less had persistent scoliosis.

Of 13 patients with chronic empyema requiring multiple operations, rib resections and excisions of the soft parts, persistent scoliosis developed in 5. These 5 patients were all in the group (9 patients) whose illness began at 12 years of age or under. In 2 of these the curvatures followed thoracoplasties, with a resultant thoracoplasty type of scoliosis, and in 3 they followed multiple rib resections, with a postempyemic type of curvature.

CONCLUSIONS

Persistent scoliosis is not a complication of acute empyema.

Persistent scoliosis frequently occurs as a complication after extensive operations on the thoracic cage for chronic empyema in children, and surgeons should take prophylactic measures against its occurrence.

The reasons for the appearance or nonappearance of persistent scoliosis are not apparent.

17 East Ninety-Sixth Street.

16 East Ninety-Sixth Street.

MULTIPLE MYELOMA

REVIEW OF FORTY CASES

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INCIDENCE

Multiple myeloma is a rare disease. Life insurance tables give its incidence as 0.03 per cent of all malignant growths or 3 per cent of all sarcomas of bone. In the American Registry of Bone Tumors its relative incidence is somewhat higher; in proportion to osteogenic sarcoma it is in the ratio of approximately 1 to 12, and to Ewing's sarcoma, of approximately 1 to 3. Of the 200 primary malignant tumors of bone seen at the University Hospital since 1925, 40 have been diagnosed as multiple myeloma, an incidence of 20 per cent. This is at marked variance with the figures usually given, the incidence of multiple myeloma at the Johns Hopkins Hospital being only 3 per cent of 400 sarcomas of bone. The 40 patients with multiple myeloma reported on here were encountered in a series of 298,546 patients admitted to the hospital, a ratio of 1 to 7,464.

GENERAL CONSIDERATIONS

Unlike osteogenic sarcoma and Ewing's tumor, which occur principally in young persons, multiple myeloma is a disease of later life. Seventy-three per cent of the tumors in this series occurred from the fifth to the seventh decade, inclusive. The average age at the time the diagnosis was made was 53 years, with a range from 28 to 73 years. The tumor in the youngest patient was verified microscopically as typical plasmacytoma. This is significant because there are only 2 reported cases of multiple myeloma in an adult under 30 years of age; Moore [1] reported a case in which the patient was 27, and Haberfeld and Lordy,[2] a case in which the patient was 22.

From the Department of Surgery, the Orthopedic Service of Dr. Carl E. Badgley, University Hospital.

1. Moore, S.: Multiple Myelomata, Radiology **5**:18 (July) 1925.

2. Haberfeld, W., and Lordy, C.: Contribução ao estudo anatomico e clinico do syndromo de Hodgkin e do myeloma, Arch. brasil. de med. **7**:431, 1917. Geschickter and Copeland.[3]

The reported cases of myeloma in children have been collected by Geschickter and Copeland,[3] and in each of these the diagnosis was open to serious question. Originally there was included in this series the case of a 15 year old boy who had multiple lesions with microscopic characteristics closely resembling those of myeloma. This case was dropped because ultimately a diagnosis of Ewing's endothelial myeloma was made.

Multiple myeloma occurs more frequently in males than in females. Of 40 patients, 25 were men, an incidence of 63 per cent.

There was a family history of some type of malignant growth in 31 per cent of cases. In 51 per cent there was no such history, and in the remaining 18 per cent it was not definitely established whether such growths had occurred.

Definite inquiry for a history of trauma elicited a negative response in 28 cases, or 70 per cent. Of the patients in the remaining 12 cases, 3 recalled an injury, but in each instance it had occurred five or more years prior to the onset of symptoms; hence it is improbable that in these 3 cases there was an etiologic relation between the trauma and the development of myeloma. In 3 cases no information regarding trauma was available. In 2 cases a minor injury initiated the symptoms of myeloma, indicating that the trauma merely called attention to the underlying lesion. In only 4 cases was there a history of trauma antedating the onset of symptoms of myeloma by less than five years, the interval in these cases varying from five to twelve months. It seems justifiable to conclude from this series that trauma plays an insignificant role in the development of myeloma.

CLINICAL CHARACTERISTICS

There was no typical clinical history of multiple myeloma. However, an analysis of the symptoms furnished a few facts of considerable interest. As has been stated, the disease occurred relatively late in life, the average age being 53 years. Pain occurred in every instance. There was nothing diagnostic in the type of pain, its location or its duration. The average interval between onset and admission to the hospital was thirteen months, the shortest period being six weeks and the longest five years. The pain was variously described as dull, aching, rheumatic, neuritic and, in a few cases, sharp and lightning-like. In 53 per cent of the cases pain was referred to the back, most often to the lumbar region. Pain in the chest or over the ribs or the sternum occurred in 25 per cent of the cases. In 55 per cent there was pain in the extremities, most often in the shoulders, hips and thighs. Pain in the lower extrem-

3. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone (Including the Jaws and Joints), revised ed., New York, American Journal of Cancer, 1936.

ities frequently was of the radiating type often associated with pain low in the back. In 1 case the only symptom was a painful defect in the skull.

Geschickter and Copeland [3] have pointed out that there is a typical course of pain in cases of multiple myeloma: a first stage, of intermittent, indefinite pains which become worse on motion or pressure; a second period, of aggravation with intense pain; a third period, of subsiding, intermittent pains; a fourth period, of relative freedom from pain with symptomatic relief, and a fifth and final stage, of recurrent, progressively intense pain proceeding to death. Only a few cases in our series could be fitted into this classification. However, the growth in more than 50 per cent ran a course characterized by three stages, namely, a period of onset, a single remission extending over a few weeks to several months and a final stage characterized by progression to the terminal event.

The appearance of tumor masses was one of the presenting symptoms in 13 cases, or 32 per cent of the total number. In 5 additional cases palpable tumors were found on physical examination, bringing the incidence up to 45 per cent. The most frequent sites of these tumefactions were the skull and the sternum. In 1 case the only symptom or sign of multiple myeloma on examination was a soft, tender defect in the skull; it was not until several months later that other lesions were demonstrable by the roentgen rays, in the spine, ribs and shoulder girdle. With this 1 exception the tumefactions in the skull were always multiple. Without exception the palpable tumors elsewhere were solitary. There were 5 cases of tumors of the skull, 5 of tumor of the sternum, 3 of tumor of the pelvis and 1 each of tumor of the orbit, the mandible, the spine, the scapula and the ribs. The tumors were tender, soft and exceedingly vascular. In 1 case there was a definite bruit; in another an attempt at removal of tissue for biopsy resulted in such a massive hemorrhage that the attempt had to be abandoned and the wound packed. The occasional observation of fluctuation in the size of a tumor may be explained on the basis of hemorrhage into the tumor with subsequent absorption of the hemorrhage.

At the time of admission to the hospital the majority of patients did not present the constitutional symptoms usually associated with malignant disease, namely, weakness, easy fatigability, anorexia, loss of weight and pallor. When such symptoms appeared, the disease was usually well advanced.

The incidence of pathologic fracture in multiple myeloma is high. However, this finding varies with the stage at which the patient is seen. Since the tumor is bone destructive, the longer the patients are followed

the higher the incidence becomes. Geschickter and Copeland [3] found pathologic fractures in 62 per cent of patients with multiple myeloma as compared with 33 per cent of patients with metastatic carcinoma and 8 per cent of patients with osteogenic sarcoma. In the present series pathologic fracture was diagnosed in 23 per cent. The fractures occurred most frequently in the ribs and clavicles. Fracture of the upper end of the femur occurred in 5 and fracture of the humerus in 2. In 1 of these the fracture of the humerus was followed by healing. Union of fractures has been reported by Meyerding,[4] Moore,[1] Bruce and others. Figure 1 shows a healed pathologic fracture of a rib.

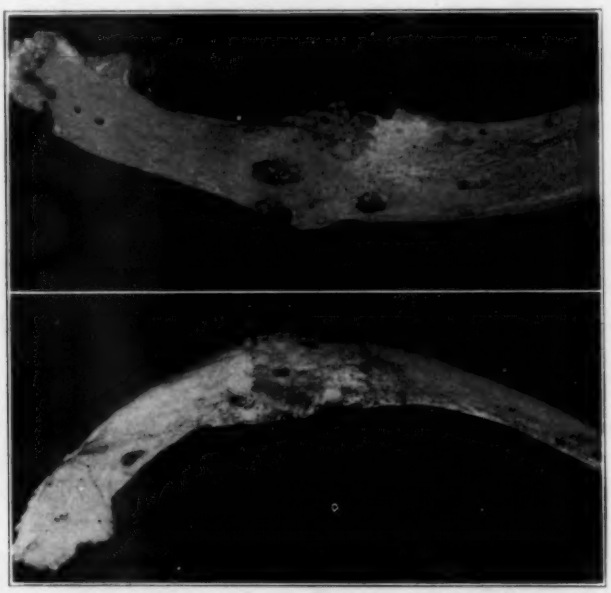

Fig. 1.—Two views of the same rib, showing healing of a pathologic fracture secondary to multiple myeloma.

The deformities produced by multiple myeloma are confined to the trunk and occasionally are found in the shoulder or in the pelvic girdle. In 7, or 18 per cent, of the patients there was a definite kyphos, in 6 in the dorsal region and in 1 in the lumbar. Three of these patients had a localized gibbus due to collapse of a single vertebral body. In the majority of patients with spinal involvement there was exaggeration of the normal dorsal kyphosis. With the destruction of the vertebral bodies there was, of course, shortening of the trunk with approximation of the ribs to the brim of the pelvis. Deformities of the chest wall took the form of tumors of the sternum (12 per cent), of the ribs or of the

4. Meyerding, H. W.: Multiple Myeloma, Radiology **5**:132 (Aug.) 1925.

clavicles. One patient had a large tumor located in the buttock, arising from the ilium. Another had a marked deformity of the head due to a tumor of the skull (fig. 2).

Involvement of the nervous system was found in 35 per cent of the patients. The most common neurologic finding was paraplegia of the lower extremities, which occurred in 7 patients, or 18 per cent. The paralysis was usually the flaccid type and was accompanied by sensory changes, with disturbances of control of the bowel and of the bladder. Typical sciatica occurred in 4 patients. In 1 patient there was radiculitis,

Fig. 2.—Unusual deformity of the head due to involvement of the skull in multiple myeloma.

with sharp, severe shooting pains in both upper extremities. In another there were similar pains encircling the thoracic cage.

LOCATION OF LESIONS

Myeloma is almost invariably multiple. In 3 patients in this series solitary involvement was found on the first admission, but subsequent studies showed multiple involvement in 2 of these; the other patient, with a solitary lesion of the right ilium, which was diagnosed by biopsy, is living and well fifty-two months after admission with no other demon-

strable lesion. By roentgen examination the skull was found to be involved in 73 per cent of the patients, the spine in 70 per cent, the ribs in 68 per cent and the pelvis in 63 per cent. The skull and spine together were involved in 53 per cent; the skull, spine and ribs together, in 38 per cent, and the skull, spine, ribs and pelvis together, in 23 per cent. The shoulder girdle, including the scapulas and clavicles, was involved in 40 per cent, the humerus in 43 per cent and the femur in 48 per cent. The humerus and femur were uniformly invaded in their proximal portion. The ulna was involved in 2 patients, the tibia in 2, the radius in 1 and the fibula in 1. It will be noted that the sites of predilection were those where there is persistent formation of blood in the adult. In no instance was involvement of the hand or foot demonstrated. However, Meyerding [4] has shown a roentgenogram of a patient in whom all of the bones of the hand were involved.

ROENTGEN FINDINGS

As usually described, the roentgen findings in cases of multiple myeloma are characteristic. These characteristic features were observed in 24 cases in this series, or 60 per cent. The individual lesions were seen as definitely circumscribed areas of decreased density, varying from a few millimeters to several centimeters in diameter. The smaller areas appeared as punched-out lesions; the larger ones, as a complete melting away of bone. Figure 3 shows typical lesions of multiple myeloma in the skull. There was no reaction about these areas of destruction. Being definitely tumors of marrow, the lesions appeared roentgenologically as typically central.

In the remaining 16 cases, or 40 per cent, it was impossible to make a definite diagnosis of multiple myeloma by roentgen examination. In several cases there was evidence of osseous reaction about the individual lesions, a finding which is more typical of metastatic malignant tumor than of multiple myeloma and has been used as a distinguishing feature. In the 3 cases of initial solitary involvement the lesions could not be distinguished roentgenographically from the changes produced by osteoporosis of the spine with wedging of the individual vertebrae, such as has been described in reports of osteomalacic diseases associated with abnormal calcium metabolism and with hyperparathyroidism. Occasionally they appeared mottled owing to the coalescence of several areas of destruction. Some of the larger lesions gave the appearance of being expansile, a thin shell remaining and enclosing the area of destruction. However, as Moore [1] has pointed out, this seeming expansion is not actual distention of the bone but the result of internal resorption with external deposition of bone. That bone formation can occur in multiple myeloma has been proved by the occasional healing of pathologic fractures as well as by microscopic examination.

LABORATORY FEATURES

The outstanding laboratory finding in cases of multiple myeloma is the presence of Bence Jones bodies in the urine. The high incidence (80 per cent) reported in the older literature has not been confirmed in recent publications. In the present series, studies for Bence Jones bodies were made in 34 cases, with positive findings in 17, or 50 per cent. In several cases in which the findings were positive, repeated examinations of the urine were necessary. In 1 case four successive

Fig. 3.—Roentgenogram showing the typical lesions of multiple myeloma in the skull. There are multiple punched-out areas of destruction with no evidence of osseous reaction about them.

tests gave negative results, whereas the fifth showed the typical cloudy white precipitate between the temperatures of 50 and 60 C., which cleared up on boiling. It is evident from this that Bence Jones bodies are often present only intermittently. As the disease progresses toward the final stage, the finding tends to become constant.

Just as the absence of Bence Jones bodies in the urine does not rule out multiple myeloma, so their presence is not pathognomonic of the disease. They have been found associated with metastatic tumors of

bone, senile osteomalacia, polyfibrocystic disease of bone, caries of the spine and leukemia (both of the lymphatic and of the myelogenous type). It will be noted that all of these conditions involve the "red marrow bones." The exact source and significance of the albuminoid substance is not known. The fact that it is found in the urine does not mean that it is due to renal damage, as was proved by autopsy on a patient in whom there was no evidence of renal damage but who showed Bence Jones proteinuria during life.

Determinations of serum calcium and phosphorus were made in one third of the cases. In only 2 cases were there definitely abnormal findings; in 1 there was a serum calcium content of 13.5 mg. and a serum phosphorus content of 7.5 mg. per hundred cubic centimeters; in the other there was a serum calcium content of 13.8 mg. and a serum phosphorus content of 3.9 mg. per hundred cubic centimeters.

All types of blood pictures have been reported in cases of multiple myeloma. In this series the most constant finding was secondary anemia, which was mild in 38 per cent, moderate in 13 per cent and severe in 23 per cent of cases. The primary anemia which has been reported occasionally and has been supposed to be due to displacement of hemopoietic tissue by tumor elements was not found. In 4 cases there was leukopenia on the patient's first admission to the hospital. In 3 cases there was leukocytosis, the leukocyte counts being 11,600, 12,500 and 15,500 per cubic millimeter respectively. Circulating plasma cells were found in 3 cases. "Blast" cells either of the lymphocytic or of the myelocytic series were found in 3 cases. How closely multiple myeloma may simulate leukemia is shown by the following case.

C. S., a 41 year old man, had noted pain in the back, head and legs for four months. Three weeks before admission he had had repeated epistaxes for which repeated transfusions were necessary. He was admitted to the hospital in coma. Roentgen examination showed destructive lesions of the spine, the skull and the ribs. No Bence Jones bodies were found in the urine. Studies of the blood showed a hemoglobin content of 28 per cent; the red cell count was 1,810,000 and the white cell count 15,500 per cubic millimeter; the differential cell count showed myeloblasts 4 per cent, myelocytes 6 per cent, metamyelocytes 11 per cent, young polymorphonuclear leukocytes 32 per cent, adult polymorphonuclear leukocytes 25 per cent, eosinophils 3 per cent, large lymphocytes 12 per cent, small lymphocytes 5 per cent and monocytes 2 per cent. A clinical diagnosis of leukemia was made. The patient died a few days after admission. At autopsy the diagnosis was multiple myeloma of the mature plasmocytoma type.

PATHOLOGIC CHARACTERISTICS

In 23 cases, or 58 per cent, the diagnosis of multiple myeloma was confirmed by pathologic study. Grossly the tumors were surrounded by a thin shell of bone which could be cut easily with a knife. The tumor tissue was dark red or grayish red, depending on its vascularity.

One tumor was virtually black, owing to the presence of old hemorrhage. As has been noted, the fluctuation occasionally seen in the size of a tumor was probably due to hemorrhage into the tumor with subsequent absorption.

Microscopically the growths in 18 of the 23 cases, or 78 per cent, were diagnosed as plasmacytoma. The typical picture was that of closely packed round cells, occurring in solid sheets with little or no intercellular stroma. The tumor tissue was rich in blood vessels, which

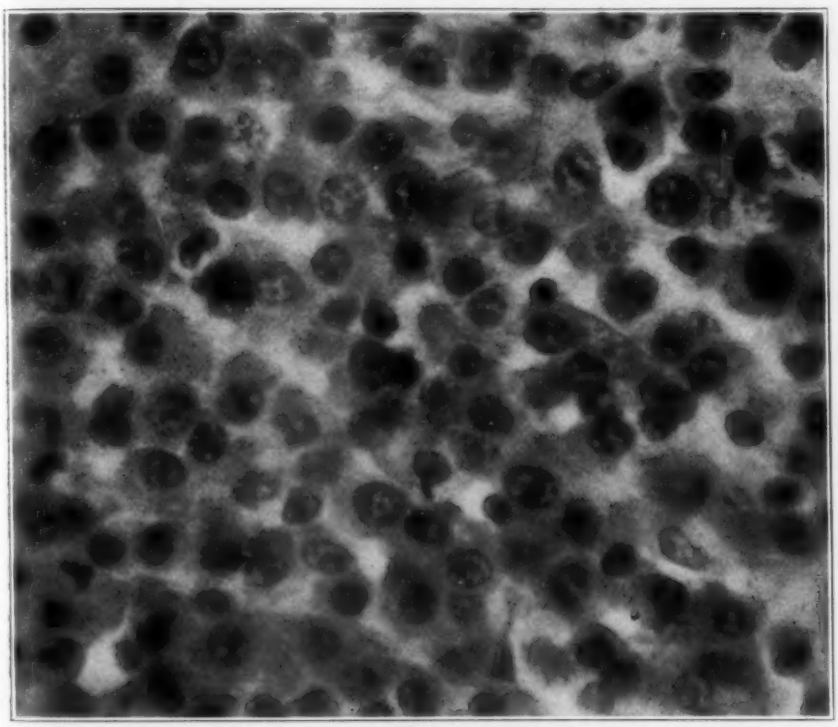

Fig. 4.—High power photomicrograph of a typical myeloma, the so-called plasmacytoma. The cells occur in solid sheets and each has an eccentric nucleus about half the diameter of the cell. Within the nucleus there is a spokelike arrangement of the chromatin. There is practically no intercellular substance.

were thin walled and lined with a single layer of endothelium. The individual tumor cells were uniform in appearance, with an eccentric nucleus about half the diameter of the cell, abundant eosinophilic cytoplasm and a spokelike arrangement of the chromatin within the nucleus (fig. 1). The nucleus had a well defined membrane within which was a nucleolus. Scattered among these cells in almost every case were smaller cells, a little more than half the diameter of the others, with scant

cytoplasm, somewhat resembling lymphocytes. Whether these cells have the same derivation as the plasma-like cells has not been determined.

In 2 cases the type of cell was identical with that observed in Ewing's sarcoma. It was about 7 to 9 microns in diameter, had a deeply staining round or oval nucleus, scanty pink-staining cytoplasm and no definite arrangement of the chromatin in the nucleus. The microscopic diagnosis in these cases was round cell sarcoma, and the diagnosis of multiple myeloma was made on characteristic clinical features.

In 1 case a diagnosis of myeloblastic myeloma was made, the cells closely resembling those of the myelocytic series. In the remaining 2 cases an unqualified diagnosis of multiple myeloma had been made previously, and the sections were not available for further examination when this study was made.

Autopsy was performed in 14 cases, or 35 per cent. In 3 of the 14 cases autopsy was done elsewhere, so that the material was not available for study. Of the remaining 11 cases, there were 6 in which myelomatous involvement of the soft tissues occurred. In the first of these 6 cases there was infiltration of the liver, spleen, lymph nodes and kidneys, with vicarious hemopoiesis in the liver, kidneys and lymph nodes. In the second case there was retroperitoneal dissemination with massive infiltration of the pancreas and invasion of the rectum, seminal vesicles, prostate and bladder. In the third case there was infiltration of the meninges, liver, kidneys and periaortic lymph nodes. In the fourth there was infiltration of the dura (from the calvarium); in the fifth, of the thyroid, and in the last case, of the liver. Thus it is evident that multiple myeloma is a disease which is not limited to the skeleton. Clinically the infiltration of extraskeletal tissues is not often noted. Metastases to the lung are unusual, contrary to the finding in other forms of bone sarcoma. In only 1 case were pulmonary metastases found; they were diagnosed by roentgen examination.

The type of renal involvement observed at autopsy was not characteristic of multiple myeloma. In 2 cases there was infiltration of the kidneys by the malignant tumor tissue. Of the 11 cases in which sections of the kidney were reviewed arteriolosclerotic nephropathy of varying severity was observed in 8, simple atrophy and calcification of the tubules in 2 and hydronephrotic atrophy in 1. The glomeruli showed relatively slight changes, usually hyaline thickening of the basement membrane or fibrosis of a few scattered glomeruli. Tubular casts were present in 5 cases. There was no evident correlation between the type or severity of renal damage and the appearance of Bence Jones protein in the urine. As has been pointed out by Bell,[5] clinical obser-

5. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, Am. J. Path. **9**:393 (July) 1933.

vations and animal experiments have shown that apparently Bence Jones protein may pass through normal kidneys.

Bell [6] has also demonstrated a more or less characteristic effect of multiple myeloma on the kidneys. There is formation of tubular casts of Bence Jones protein that obstruct the tubules and cause proximal tubular atrophy. When large numbers of tubules are obstructed, extensive atrophy of the cortex and renal insufficiency ensue. A comparable picture was found in only 1 case in this series.

TREATMENT

Since the prognosis for life is hopeless, it is customary to indicate that treatment is chiefly symptomatic and that in certain cases roentgen therapy may be helpful in controlling pain. In the present series, however, two things deserve special mention, namely, the effect of roentgen therapy on the duration of life and the treatment of paraplegia.

It is generally recognized that the use of roentgen therapy for multiple myeloma results in symptomatic improvement with relief of pain. Of the 40 patients studied, 23, or 58 per cent, received roentgen therapy. Seventy-eight per cent of these had definite relief from pain; as to the remainder, no information regarding this point was available. As administered by the department of roentgenology, the doses of radiation were equivalent to single doses of 600 roentgens (r) to each area. In a number of instances the radiation was fractionated into doses of 200 r each. The factors of treatment were a filter of 0.9 mm. of copper (a half value layer) with the tube at a distance of 50 cm. from the skin and an intensity of 30 to 50 r per minute. The treated areas varied from 100 to 400 sq. cm.

Symptomatic treatment without roentgen irradiation was administered to 17 patients. In this group the average duration of life after admission to the hospital was six months. On the other hand, the group which received roentgen therapy had an average duration of life after admission of twenty-three months. The latter group includes 5 patients who are still living at the time of this report, so that the difference in the average periods of survival will become greater until all the patients have died.

In the symptomatically treated group 4 patients died within a few days after admission. When these 4 are omitted from the comparison, the average period of survival after admission was eight months for the 13 patients who received symptomatic treatment. Further study showed that these 13 patients were seen, on the average, four months later in the course of the disease than were the group treated by roentgen irradiation. By eliminating the differences due to the stage at which treatment was started, it was found that the patients treated with

roentgen rays lived twenty-three months after admission and treatment, as compared with a twelve month survival for the patients who did not receive roentgen therapy.

In 1933 Jacox and Kahn [6] reported on 2 patients who had multiple myeloma with involvement of the spinal cord and who were treated by laminectomy and roentgen therapy. At the time of their report both patients were free from symptoms and working daily. One of them died on Aug. 9, 1936, eight years and six months after admission (nine years and six months after the onset of symptoms). The other died of pneumonia on April 3, 1934, thirteen months after admission, after a complete recovery from motor paralysis of the lower extremities and sensory paralysis below the fifth dorsal segment.

Since 1933, 3 additional patients have been treated by laminectomy at the University Hospital.

Fig. 5.—Solitary myeloma with the pathologic characteristics of plasmacytoma. *A*, melting away of a portion of the acetabulum and ilium. The patient was given roentgen therapy. *B*, result forty-nine months later. There are evidence of healing and intrapelvic protrusion of the head of the femur. The patient is living and well fifty-two months after the institution of treatment.

G. H., a 64 year old man, had complete motor paralysis of both lower extremities of four weeks' duration, with sensory paralysis beginning at the level of the fourth dorsal segment and involvement of the bladder. Roentgen examination showed involvement of the fourth dorsal vertebra and of the ribs. On April 8, 1935 a decompressive laminectomy was done, with partial excision of a grayish red gelatinous tumor. Microscopically the lesion was a plasmacytoma. There was a gradual return of motor and sensory function, but the patient died on the forty-fourth postoperative day of a massive facial infection and pneumonia.

M. W., a 62 year old man, was admitted to the University Hospital on Feb. 26, 1934, the chief complaint being paralysis of the lower extremities. During the two months prior to admission there had been pain between the scapulas

6. Jacox, H. W., and Kahn, E. A.: Multiple Myeloma with Spinal Cord Involvement, Am. J. Roentgenol. **30**:201 (Aug.) 1933.

and in the left upper anterior part of the chest. Ten days prior to admission the patient noted numbness from the waist down, associated with motor paralysis of the lower extremities; during this same interval there was complete retention of urine, and daily catheterizations were necessary. Examination revealed sensory paralysis beginning at the level of the second dorsal segment and spastic paralysis of the lower extremities. Roentgen examination showed gross destruction of the second dorsal vertebra. On February 28 a decompressive laminectomy was done, with partial excision of a grayish soft vascular tumor projecting into the spinal canal from the second dorsal vertebra. Three weeks later roentgen therapy was

Fig. 6.—Lateral view of the spine, showing complete disappearance of the third lumbar vertebra. The small flake of calcium between the second and the fourth lumbar vertebra is all that remains of the third lumbar vertebra. There is posterior displacement of the second lumbar vertebra on the fourth. A laminectomy had been performed for paraplegia, followed by roentgen therapy. The pathologic diagnosis was plasmacytoma.

started, a total dose of 1,600 r being given over a period of seven weeks. Immediately after the operation the paraplegia began to improve. One month after the operation the patient was able to walk with crutches; two months later he could walk with a cane, and thereafter he was able to resume work. The vesical difficulty disappeared completely. This patient died on July 29, 1938, four years

and five months after laminectomy, of lobar pneumonia, with no recurrence of the paraplegia or of the associated vesical symptoms. Autopsy confirmed the diagnosis of multiple myeloma.

U. K., a 60 year old woman, complained of pain in the back of twenty-six months' duration. During the four weeks previous to admission she noted weakness of both lower extremities, inability to walk, sensory paralysis beginning at the level of the first lumbar segment and considerable difficulty in micturition. Roentgen examination showed involvement of only the eleventh dorsal vertebra. A laminectomy was done on July 29, 1938, and a grayish soft tumor was encountered projecting from the body of the eleventh dorsal vertebra. Partial resection of the the tumor was carried out, with removal of the laminas of the tenth to the twelfth dorsal vertebrae. Microscopic examination showed a plasmacytoma. One week after operation the patient was given a course of roentgen therapy, the total dose being 1,200 r. One month later she was discharged with complete sensory recovery, normal function of the bladder and of the bowel, and increasing motor power in the lower extremities. One month later she had resumed walking. On November 30, four months after operation, she reported herself as well.

With the exception of the 1 patient who died postoperatively of an unrelated infection, laminectomy followed by roentgen therapy was eminently successful in these cases of involvement of the spinal cord. Dr. E. A. Kahn has called attention to the fact that in the presence of severe compression of the cord, laminectomy should always be done before roentgen therapy is given. This permits the establishment of a positive diagnosis and prevents further damage to the cord by swelling subsequent to irradiation.

PROGNOSIS

Multiple myeloma is invariably fatal, there being no permanent cure on record in a case in which the diagnosis was proved. Geschickter and Copeland stated that the average duration of the disease is two years and that the longest duration of the disease in any case proved to be one of multiple myeloma was five and one-half years. They stated further that the duration of the disease appears to be uninfluenced by treatment.

In this series 35 of the 40 patients have died, with an average duration of the disease from onset of symptoms until death of twenty-seven months. The average period from admission to death for these 35 patients was fourteen months. Of the 5 living patients, 1 is living and well fifty-nine months after the onset of symptoms; 2 are living with evidence of improvement at twenty-eight and seventy-two months, respectively, and 2 are living with evidence of progression of the disease at thirteen and forty-three months, respectively. The average duration of the disease in the living patients is forty-three months. The average duration in the entire series, living and dead, from onset until death or date of writing, is twenty-eight months; from admission to death or date of writing it is fifteen months. Obviously, these figures will increase until all the patients have died.

Although a five year period of survival is considered unusual for a patient with multiple myeloma, 5 patients in this series, or 12.5 per cent, lived longer than five years. Four of these died after surviving one hundred and seventy-two, one hundred and seventy-four, seventy-eight and sixty-one months, respectively, from the onset of symptoms until death. One patient is living with evidence of improvement after seventy-two months. As has been noted, 1 patient is living and well fifty-nine months after the onset of symptoms. In all of these cases the diagnosis was proved by microscopic examination, except in the 2 in which the patients survived for seventy-eight and seventy-two months, respectively. These 2 had typical roentgen characteristics of multiple myeloma with Bence Jones proteinuria.

The patient who lived fourteen years and four months was a 49 year old woman who was admitted to the University Hospital on Oct. 1, 1928, complaining of pain in the left hip of five years' duration.[7] Roentgen examination on admission showed destructive lesions in the left ilium and in the left femur. On October 20 a biopsy of material from the left ilium was done, which showed a myeloma of the plasma cell type. The patient was treated by roentgen irradiation and was discharged as improved. Subsequently she had destructive lesions in the skull, clavicle, scapula, ribs, spine, pubis and right humerus. Bence Jones protein, which had been absent from the urine on the first admission, was observed. In 1931 roentgen therapy was resumed, and it was given at intervals to the time of death, always with symptomatic improvement. In 1934 a biopsy was done elsewhere of material from a lesion of one of the ribs, which was also reported as myeloma. The patient died on Feb. 4, 1938, almost ten years after the first admission.

The patient who lived nine and one-half years was the one described in the first case reported by Jacox and Kahn. Treatment was by laminectomy and roentgen irradiation.

An attempt was made to evaluate the various factors which might influence the prognosis of multiple myeloma. The cases were divided on the basis of duration of symptoms previous to admission into three groups: group 1, duration of symptoms up to six months; group 2, duration of symptoms from six to twelve months; group 3, duration of symptoms over twelve months. In the first group, which comprised 14 cases, the average survival period was thirteen months after admission to the hospital. In the second group, which comprised 20 cases, the average survival period was sixteen months after admission. In the third group, which comprised 6 cases, the average survival period was twenty-seven months. From this it would seem that early diagnosis is of no benefit to the patient. Perhaps the proper explanation is that the more

7. This case is to be reported in a separate publication.

rapidly lethal the malignant process is, the more quickly it drives the patient to his physician because of the severity of the symptoms.

The average age of the patients in this series was 53 years. The average total duration of the disease in the 18 patients under 53 years of age was thirty-five months; in the 22 patients over 53 years of age the average total duration of the disease was twenty-two months. The 2 youngest patients in this series, aged 28 and 32 years, respectively, are living with no evidence of progression of the disease at fifty-nine and seventy-two months, respectively, after the onset of symptoms. The conclusion from this series is that the younger the patient the better the prognosis in terms of the period of survival.

Three patients presented themselves with solitary lesions on the first admission. Two of these subsequently had multiple lesions. The first lived nine years and six months after the onset of symptoms; the second lived four years and seven months. The other patient is living and well fifty-nine months after the onset of symptoms, with no evidence of multiple lesions. To date the average total duration of the disease in these 3 cases is seventy-six months, as compared with the average total duration of twenty-four months in the remainder of the series.

The effect of treatment on the prognosis of multiple myeloma has been discussed in the section on roentgen therapy. The patients who received roentgen therapy lived on the average twice as long as those who did not receive it. Of the 5 patients in whom the total duration of the disease was over five years, 3 received roentgen therapy and two did not. The 2 who were not treated died one month and eighteen months, respectively, after admission. Each of the other 3 lived more than five years after admission, the average period from admission until death being eighty-seven months. It appears that roentgen therapy prolongs life in addition to controlling pain.

SUMMARY AND CONCLUSIONS

Multiple myeloma is a rare disease. It is a disease of middle and late life, the average age of the patients in this series being 53 years. It occurs almost twice as frequently in men as in women. Etiologically it is not related to trauma. Its chief symptom is pain, which may occur in any location and is not in any way characteristic except that there is usually a single period of remission. Palpable soft tumors are found in one half of the patients, usually on the skull or on the trunk. Pathologic fractures are common. Deformities of the thoracic cage and of the spine are not unusual. Paraplegia and nerve involvement referable to the spinal cord constitute frequent complications. Multiple myeloma occurs most frequently in the skull, spine, ribs and pelvis, in that order. Solitary lesions are rare and usually become multiple before death.

Roentgen examination shows multiple punched-out areas of osseous destruction with no evidence of osseous reaction. The laboratory findings show secondary anemia of varying severity and, in one half of the cases, Bence Jones protein in the urine. Microscopically the lesions show masses of round cells closely resembling plasma cells, with little or no intercellular substance. Autopsy reveals that in one half of the cases the soft tissues, particularly the liver, spleen and kidneys, are invaded by myeloma. The renal findings at autopsy are not characteristic, arteriolosclerotic nephropathy being present in most cases. Treatment in the past has been chiefly symptomatic, but roentgen therapy gives relief from pain and prolongs life. Laminectomy and decompression of the spinal cord are indicated in cases of paraplegia due to multiple myeloma. Multiple myeloma is invariably fatal, the average duration of the disease from the onset of symptoms until death being two and one-half years. Survival for five years is an occasional occurrence. The longest period of survival on record in a proved case is fourteen years and four months. The prognosis is more favorable for relatively young patients and for those with initial solitary involvement. The prognosis is favorably influenced by roentgen therapy and, in cases of paraplegia, by decompressive laminectomy.

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CAUSAL SIGNIFICANCE TO TRAUMATIC OSSIFICATION OF THE FIBROCARTILAGE IN TENDON INSERTIONS

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Growths of bone tissue in muscles and in their tendinous insertions after trauma, in muscle tissue about joints after dislocations or in soft tissues about a simple fracture of a bone or after a minor injury commonly are given such designations as traumatic myositis ossificans, parosteal callus or some other appropriately descriptive term. Summaries of the data on such growths have been written by Fay,[1] Painter,[2] Lewis,[3] Carey,[4] Gruca,[5] von Dittrich,[6] Goto,[7] Geschickter[8] and others. All these reviews have emphasized trauma as the initiating factor. No age group is immune, but the incidence is greatest in young men. Fay stated that this indicates merely the frequency of trauma in a group leading an active life. The usual sites of these traumatic osseous growths are those exposed to injury in occupation, avocation or accident. According

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From the Henry Baird Favill Laboratory of St. Luke's Hospital.

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to Cahier,[9] three fifths of the bone formations in muscle have no attachment to the adjacent bone; the remainder are connected with it by a pedicle.

The theories compiled by Carey include practically all those which have been offered in explanation of these intramuscular growths of bone. They are (1) the hemic theory, which assumes the transformation of an organized hemorrhage into cartilage and bone; (2) the theory of proliferation of aberrant sesamoid bone tissue following trauma; (3) the theory of growth of detached flaps of periosteum into bone; (4) the theory of dissemination of osteogenic cells and proliferation through a tear of the limiting periosteum; (5) the theory of hematogenous infectious myositis; (6) the theory of the escape of synovia into the soft tissues, with organization; (7) the theory of metaplasia of intramuscular connective tissue into bone; (8) the theory of combined metaplastic and periosteal tissue growth, and (9) the theory of an individual diathesis or dyscrasia. Pertinent objections confront these explanations. There is little evidence that the bone growths are neoplastic, although pathologists sometimes have mistaken the tissues for sarcoma. Factors (other than the immediate trauma) influencing the development of these bone tissues, according to Wagner,[10] are a shift to alkalinity of the tissue fluids, the growth of connective tissue cells and the activity of an enzyme that splits phosphoric acid from organic compounds.

The clinical course of traumatic ossification has been arranged into three stages.[11] At first the symptoms of trauma to the tissues are dominant, but the disability produced by the injury does not subside. After the second week, pain reappears, the local swelling increases and the tissues become indurated. In the third or fourth week roentgenograms disclose a density in the soft tissues, which gradually assumes the characteristics of bone. As a rule there is no fever.

Histologic examination in the first stage demonstrates acute exudative inflammation of the tissues, edema and hemorrhage, the immediate sequelae of the trauma. Later there is scarlike connective tissue or granulation tissue with masses of bone and cartilage in varying amounts and residue of skeletal muscle. Gruca stated that the plates of bone arise directly from the connective tissue or indirectly from the connective tissue through a cartilaginous stage. The skeletal muscle fibers have no active part.

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9. Cahier, L.: Sur les myostéomes traumatiques, particulièrement sur leur pathogénie et leur traitement opératoire, Rev. de chir. **29**:356, 1904.

10. Wagner, W.: Beitrag zur Behandlung der Myositis ossificans circumscripta, Arch. f. klin. Chir. **172**:543, 1933.

11. Heidrich, L.: Röntgenbestrahlung bei der Myositis ossificans circumscripta, Arch. f. klin. Chir. **170**:256, 1932. Gruca.[5]

A number of specimens of such intramuscular bone tissue in various stages have been encountered in routine examinations of surgical material at St. Luke's Hospital.

REPORT OF CASES

CASE 1.—A white man aged 35 had noticed for a year a painless mass in the muscles of the calf of his right leg and a similar but larger mass above the first for about two months. They had not increased appreciably in size. The only relevant injuries recalled were several blows on the muscle of the calf with a bowling ball within the past four years. On Jan. 4, 1932, the two pieces of hard tissue, measuring respectively 5.5 by 3.5 by 1 cm., and 4.5 by 2.5 by 1 cm., were removed by Dr. H. E. Jones. Seventeen months later another mass, 3 by 3 by 1.5 cm., was removed from the medial portion of the belly of the right gastrocnemius muscle. This had been present for a few months in the old scar.

The tissue removed on Jan. 4, 1932 contained differentiated lamellar bone. The narrow, compact trabeculae enclosed wide marrow spaces filled with fat. A thin fibrous capsule along the margins contained atrophied muscle fibers. Cartilaginous tissue was not present in the portions examined. The tissue removed on May 31, 1933 had less differentiated bone. Bone trabeculae were embedded in dense fibrous tissue that included atrophied and unchanged skeletal muscle fibers. Peripheral portions of the trabeculae had lamellar bone, and irregular regions near the centers were differentiated incompletely and contained basophilic granular material.

CASE 2.—A mass of fibrous, muscle and bone tissue 2 by 1.5 by 1.4 cm. was removed from the muscle tissues anteriorly near the center of the upper part of the right arm of a man aged 53 by Drs. H. E. Mock and J. D. Ellis. A matrix of fibrous stroma had trabeculae of compact bone. Some trabeculae merged into irregular masses of hyaline cartilage with large lacunae (fig. 1*A*). The associated dense scar tissue contained atrophied skeletal muscle fibers.

CASE 3.—The lower third of the left thigh of a Negro aged 40 was bruised on March 4, 1925 by a heavy iron casting. He was incapacitated six weeks because of the painful swelling. The inflammation subsided, but a hard mass remained. On June 2 Dr. C. W. Hopkins removed soft, porous bone tissue. It was broken into small pieces. Thirty-five to fifty of these, with attached muscle and fibrous tissues, forming a mass 9 by 8 by 2 cm. which weighed 39 Gm., were submitted for routine examination.

Trabeculae of bone were embedded in edematous fibrous tissue with and without skeletal muscle fibers. Some of the bone tissue had a lamellar structure; some had a granular or hyaline matrix. These at suitable levels were continuous into hyaline cartilage with a fibrocartilage margin.

CASE 4.—A white man aged 39 fell on Jan. 27, 1929, dislocating his left elbow. There was no fracture, but for two months he had a swelling in the left cubital fossa. Flexion was limited. On August 6 Dr. W. F. Lyon removed a cylindric piece of bone 7.3 by 3.5 by 2 cm. that extended from the ulna into the brachialis muscle. The histologic preparations contained trabeculae of differentiated bone and wide marrow spaces with fat and edematous fibrous tissue. Masses of fibro-

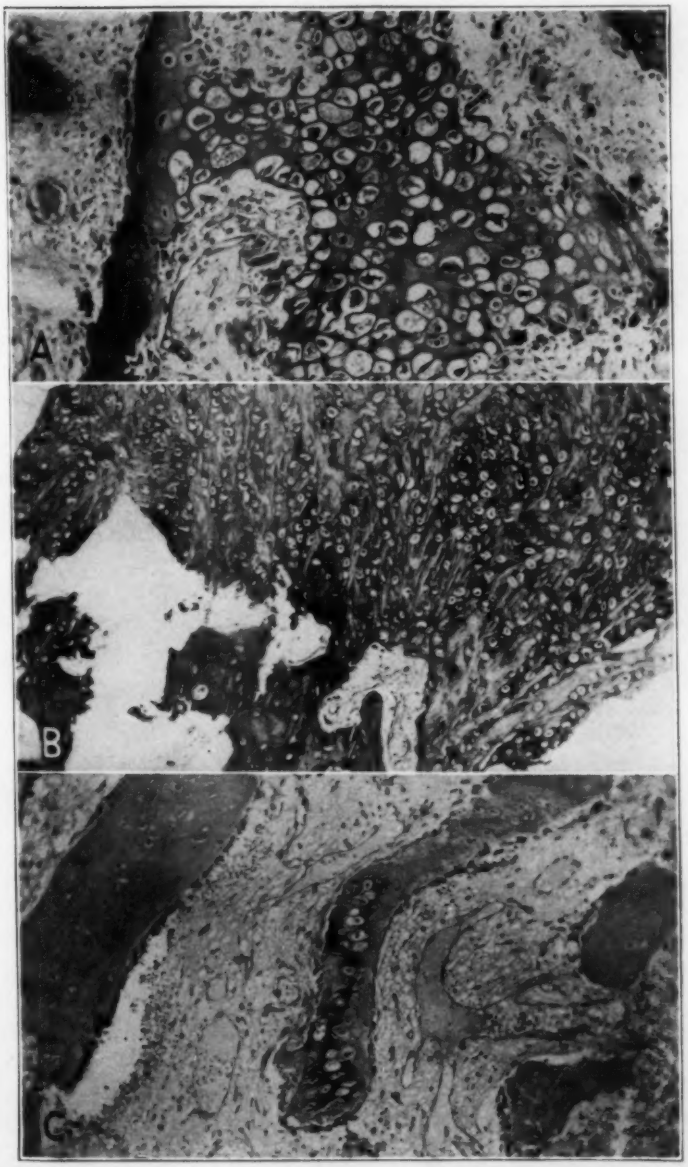

Fig. 1.—*A*, masses of hyaline cartilage continuous with bone trabeculae (case 2); *B*, masses of fibrocartilage extending into bone trabeculae (case 4); *C*, bone tissue with cartilaginous residue (case 7); × 99.

cartilaginous tissue along the margin of the bone merged directly with the trabeculae (fig. 1 *B*).

CASE 5.—While playing football in November 1931, a youth aged 18 was struck on the posterior surface of his right thigh. Swelling and slight induration of the tissues developed. On May 5, 1932, Dr. E. L. Ryerson removed a mass of bone loosely attached near the center of the posterior surface of the right femur. A piece from the attachment of the bone to the femur measured 2 by 1 by 0.7 cm.; the main portion was 7 by 2.7 by 0.5 cm. Another mass measured 3.8 by 1.7 by 1.3 cm.; broken fragments together equaled a mass 3 by 3.5 by 1 cm.

Portions from the attachment of the bone to the femur had marginal scar tissue that extended into cartilage or fibrocartilage (fig. 2 *A*), directly continuous with bone trabeculae. Some of these bone trabeculae had residues of hyaline cartilage. The main mass of bone was similar. Some of the trabeculae were osseous cartilage (fig. 2 *B*); others were incompletely developed bone (fig. 2 *C*). Loosely arranged fibrous connective tissue filled the interstices between the trabeculae.

CASE 6.—The right thigh of a Negro aged 29 was struck by an automobile. A swelling anteriorly in the middle third of the thigh became hard. After three and one-half months the mass was excised by Dr. H. E. Mock. There were many broken pieces of bone. Two of these were 6.8 by 2 by 1.5 cm. and 5.5 by 1 by 1.2 cm. respectively. The remainder equaled a mass 8 by 6 by 3 cm.

Many trabeculae were lamellar bone; others had irregular residues of ossifying cartilage (fig. 3 *B*). Islets of cartilage or fibrocartilage mingled with the bone (figs. 3 *A* and 3 *C*). Some of the bone trabeculae along the margins extended into masses of fibrocartilage continuous with organizing scar tissue. Vascular fibrous tissue was between the trabeculae.

CASE 7.—A white man aged 24 was kicked accidentally on the front of the left thigh. A small, slightly painful swelling resulted and was treated with ultraviolet rays for ten days, when it became large. About a pint of serosanguineous fluid was removed. After a few days several more ounces were removed, but no fluid was recovered a week later. Roentgenograms at this time had no unusual shadows, but after three weeks a density was demonstrated in the soft tissues. A small piece removed surgically was diagnosed as osteofibrosarcoma. The patient was admitted to St. Luke's Hospital in the care of Dr. H. E. Mock five weeks after the injury. Skeletal muscle containing a Y-shaped piece of bone was removed from the front of the middle third of the left thigh. The bone was 12 cm. long and 7.5 cm. wide. One limb had diameters of 3.5 and 2.2 cm.; the other, of 4 and 3.2 cm. A mass of bone at the bifurcation was 3 by 2.5 by 1.5 cm. A severed pedicle on one side of the Y-shaped piece was 7.5 by 1.5 cm. Another flat piece of bone was 7.5 cm. long, 3 cm. wide and 1.1 cm. thick. One side was continuous with the pedicle of the Y-shaped tissue; the other was the femoral attachment. Two pieces of bone and muscle tissue were 4 by 2.8 by 0.8 cm. and 2.2 by 1.2 by 0.5 cm. respectively.

Most of the trabeculae in the portions examined were lamellar bone; a few contained small masses of cartilage (fig. 1 *C*). The associated edematous fibrous and fat tissues had a few skeletal muscle fibers.

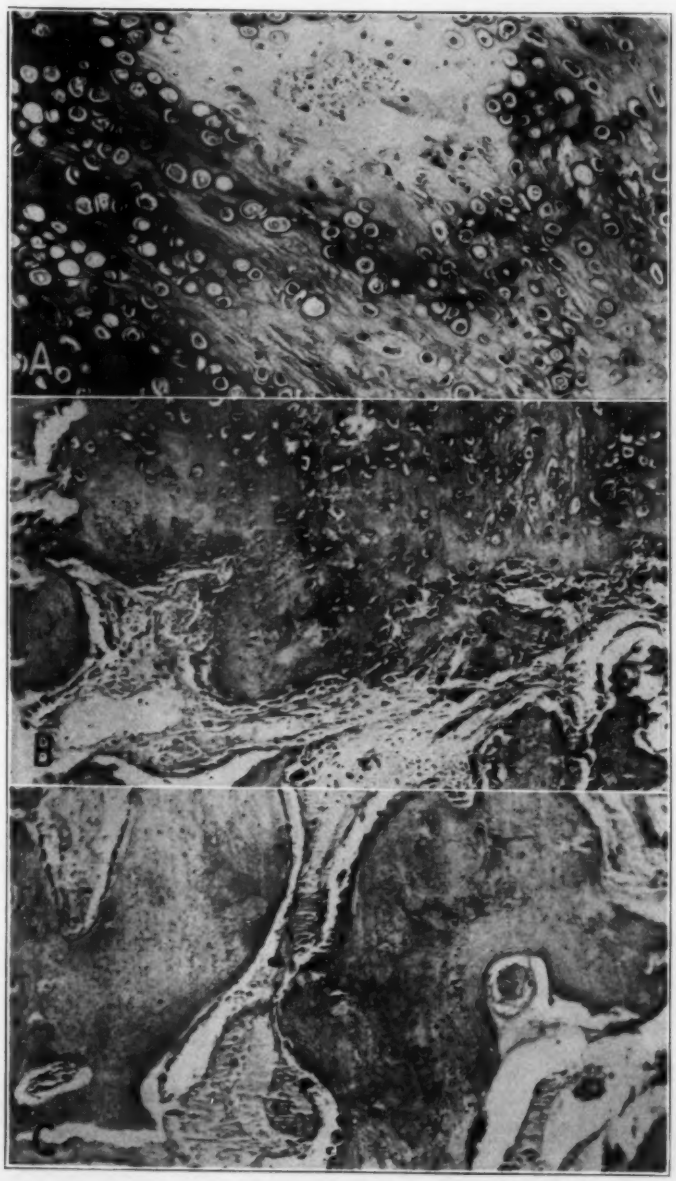

Fig. 2 (case 5).—*A*, fibrocartilage merging with bone in the femoral attachment of the callus; *B*, ossifying cartilage; *C*, incompletely differentiated bone; × 99.

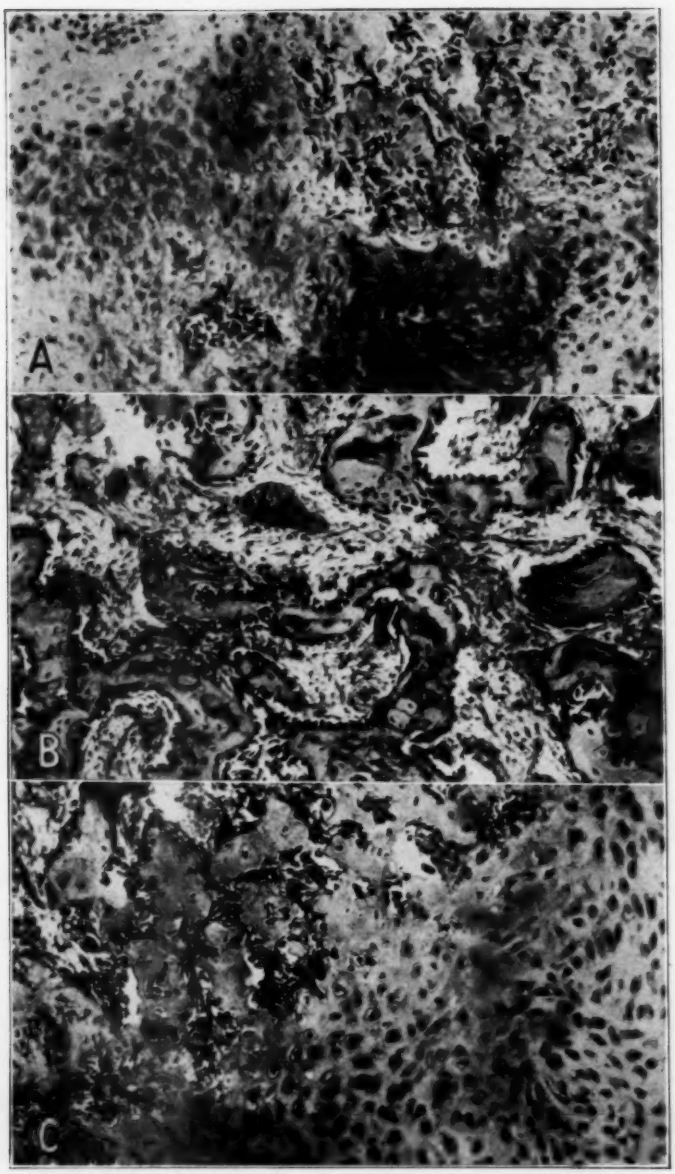

Fig. 3 (case 6).—*A*, fibrocartilage and hyaline cartilage extending into ossifying trabeculae; *B*, trabeculae of bone with residue of cartilage; *C*, cartilage merging with osseous tissue; × 99.

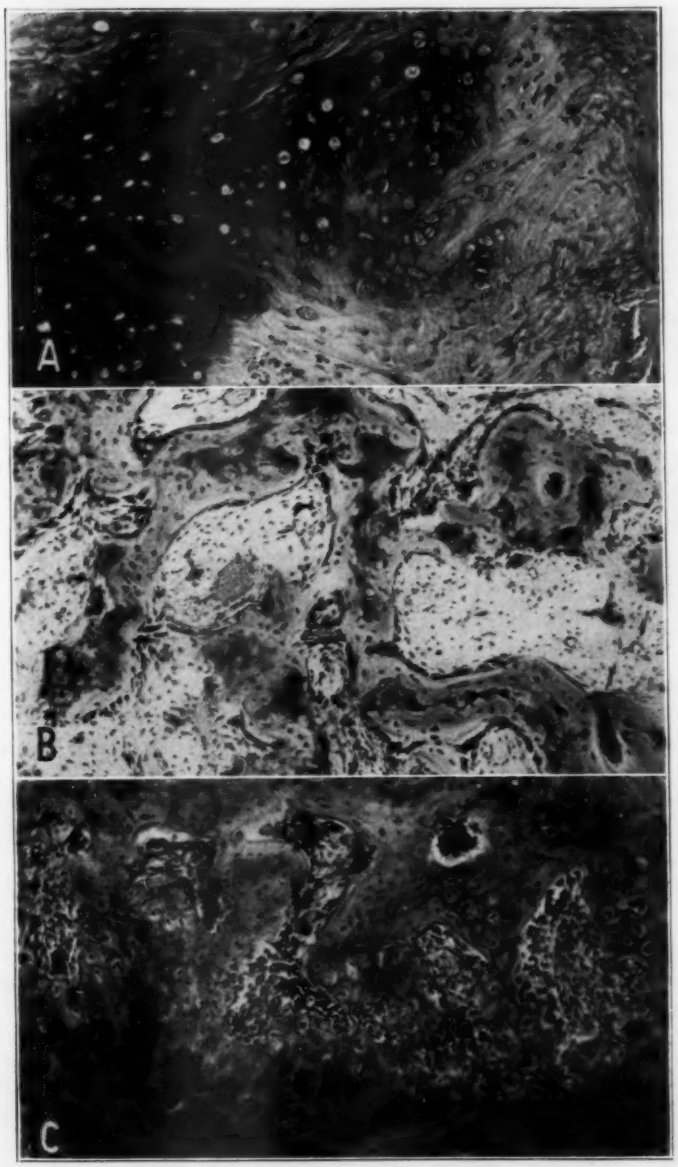

Fig. 4.—*A*, masses of fibrocartilage which extended into bone (case 8); *B*, trabeculae with residue of cartilage (case 9); *C*, cartilaginous tissue merging with osseous trabeculae (case 9); × 99.

CASE 8.—The right thigh of a white youth aged 17 was bruised during a basketball game. The muscle tissues in front became swollen and indurated. After two and one-half months an irregular mass of bone and skeletal muscle 9 by 5.5 by 2.5 cm. was removed by Dr. H. B. Thomas. Portions of the mass were fibrous or skeletal muscle tissue containing hard and soft bone; others had the consistency of cartilage. Six smaller pieces of bone also were removed.

Irregular masses of cartilage or fibrocartilage continuous with dense scar tissue extended into poorly differentiated bone (fig. 4 *A*). Many trabeculae contained large residues of a cartilage matrix. The portions between were edematous fibrous tissue.

CASE 9.—A white man aged 49 dislocated his right shoulder. With the clinical diagnosis of myositis ossificans, bone tissue was removed by Dr. W. R. Cubbins from the region of the shoulder sixty-seven days later. Six pieces of tissue ranging between 4 by 1.5 by 2 cm. and 1 by 0.5 by 0.5 cm. were submitted for histologic examination.

This tissue showed various stages of osseous growth and differentiation. There were differentiated bone trabeculae, others with residues of a cartilage matrix (fig. 4 *B*) and columns of hyaline cartilage merging into fibrocartilage (fig. 4 *C*). The cartilaginous trabeculae had traces of a fibrillar structure. Fibrocartilage constituted a large part of the tissue.

CASE 10.—A Negro aged 43 had a straight transverse fracture without dislocation of the distal third of the left radius. A cast was applied for three weeks. After two and one-half months the left forearm still was swollen and stiff. A shadow about the bone in the roentgenograms suggested a sarcoma. A section of bone tissue 4.3 cm. long and 2.5 cm. wide, chiseled by Dr. W. R. Cubbins from the cortex of the radius, extended into a ridge of bone 3.5 cm. long, 1.5 cm. wide and 1.2 cm. thick. Another section of bone tissue was 9 by 0.9 by 0.5 cm.; small pieces equaled a mass 3 by 3 by 1.5 cm.

The piece of tissue removed from the radius was cut into five blocks for histologic examination. A large amount of fibrous scar tissue covered the bone. Many trabeculae were lamellar bone; some had residues of a cartilage matrix. Masses of fibrocartilage along the edge were continuous with bone. The trabeculae near the fibrocartilage were not fully differentiated and had residues of fibrocartilage. The central portions of the mass had large amounts of fibrocartilage that merged directly into trabeculae of undifferentiated and lamellar bone (fig. 5 *A*). Many had residues of cartilage.

CASE 11.—A white man aged 38 had symptoms of obstruction of the lower part of the bowel. On Sept. 24, 1938, Dr. W. R. Cubbins resected a carcinoma in the distal portion of the sigmoid through a suprapubic midline incision. Two pieces of mucosal tissue measuring respectively 3.5 by 3 by 2 cm. and 2 by 1 by 0.7 cm. were removed on October 20 from the colostomy opening. The sections contained aggregates of carcinoma cells and a small mass of bone several millimeters in maximum diameter. The slender bone trabeculae were poorly differentiated. Many had a fibrillar matrix (fig. 5 *C*) resembling fibrocartilage; some had small masses of cartilage (fig. 5 *B*).

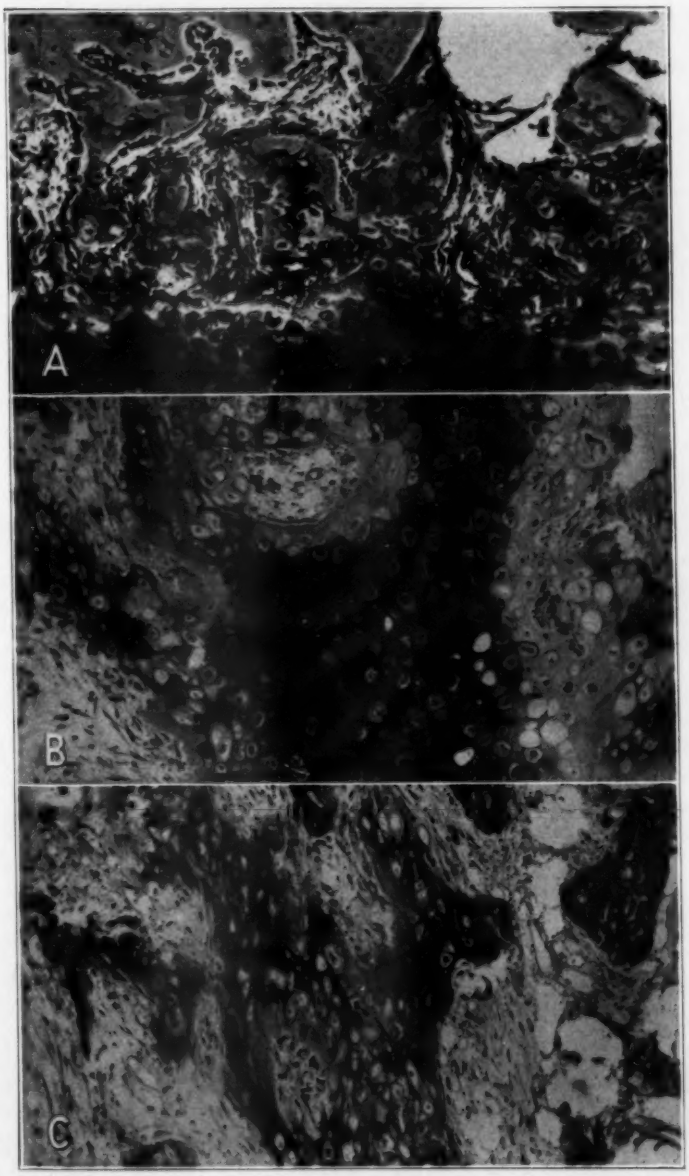

Fig. 5.—*A*, cartilaginous tissue extending into trabeculae of bone with residue of cartilage (case 10); *B*, cartilage and ossifying trabeculae (case 11); *C*, ossifying trabeculae with a fibrillar matrix (case 11); × 99.

Cartilage and fibrocartilage occurred in varying amounts in the callus tissues examined. The amount, distribution and structure seem to depend on the stage of growth. In an old callus composed of lamellar trabeculae of bone no cartilage tissue, or only traces of it, remained. Large amounts of cartilage or fibrocartilage were observed in callus tissues of recent origin. In the reviews of traumatic ossification mentioned, the presence of cartilage suggested the possibility of endochondral bone formation. This tissue usually was considered incidental in the development of the callus or metaplastic in intramuscular connective tissue. Goto expressed the belief that the formation of cartilage depends on osteogenic cells. According to Lauche,[12] all fractures of bones were believed to heal through a cartilaginous stage of callus formation. Studies of healing fractures in human and other animal bones have demonstrated that the callus with complete immobilization contains no cartilage. This tissue develops, however, when the fractured ends grate on each other, that is, when the callus at the fracture is injured by motion. Cartilage is present regularly in the callus about fractures of ribs. These differences in the cartilage content of tissues in healing fractures suggest the possibility that cartilage develops from some component other than bone. The fate of cartilage tissue in a callus may be one of several. Usually, according to Lauche, it is transformed by endochondral ossification into lamellar bone. In his discussion of the cartilaginous tissue in parosteal callus, Lauche conceded that such tissue may develop without the stimulus due to motion.

The tissue of traumatic ossification in the early stages of growth has considerable cartilage (cases 8, 9, 10 and 11). These growths have cartilage in direct continuity with partially differentiated trabeculae of bone, as well as trabeculae with residues of a cartilage matrix. The theories proposed for the origin of parosteal callus tissues and reviewed in the introductory paragraphs of this report vary widely in view and probability. None emphasizes the fibrocartilage and cartilage components as stages in the formation of the bone. If fibrocartilage is basic in the evolution of the parosteal tissues, there should be normally in regional tissues a similar matrix which, reacting to trauma by reparative growth, develops into the ossifying lesion. Such a direct process would explain more satisfactorily the actual conditions encountered.

According to textbooks on histology,[13] fibrocartilage occurs, among other places, in the ligamentum teres femoris and in the attachments of certain tendons to bones. Because many of the parosteal callus tissues

12. Lauche, A., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1937, vol. 9, pt. 3.

13. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1935, p. 116.

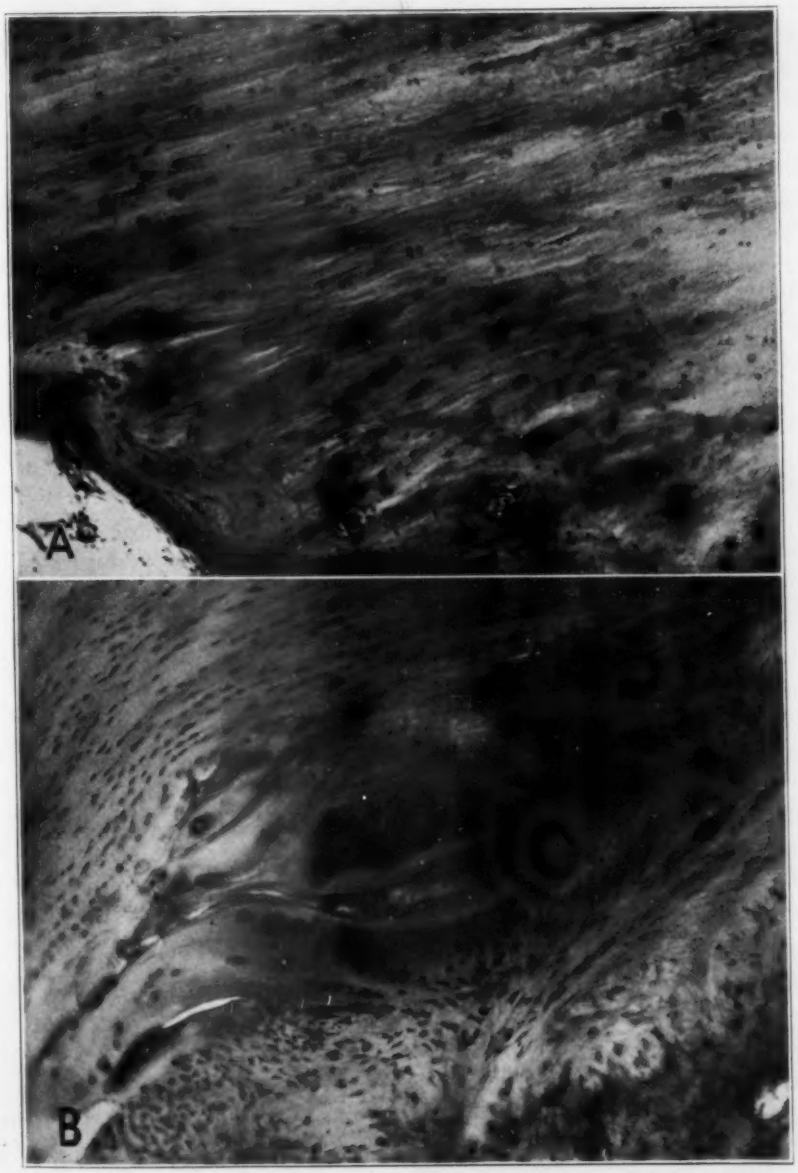

Fig. 6.—*A*, latent fibrocartilaginous tissue in the insertions of tendons from adults; *B*, latent fibrocartilaginous tissue in the insertions of tendons from adults; × 111.

occur in tendon attachments, a search was made therein for fibrocartilage. Tendon insertions with a thin plate of bone of the brachialis anticus, biceps brachialis, semitendinosus, semimembranosus, quadriceps femoris and gastrocnemius muscles were removed from 25 cadavers, male and female, the patients having died from various causes at ages between 0 (full term delivery) and 76 years. The tendons were cut 1 to 2 cm. from their insertions. The tissues of 69 tendons were fixed in Zenker's solution, decalcified and embedded in pyroxylin (celloidin), and the sections were stained with hematoxylin and eosin (some with phosphotungstic acid and hematoxylin). The tendons of infants had compact parallel collagenous fibers. Between the fibers were numerous stellate fibroblasts with oval vesicular nuclei. At a point 1 to 2 mm. from the attachment to the bone, compressed cartilage cells lay between the tendon fibers. Near the bone the tissue was dense fibrocartilage with a considerable hyaline matrix. In the adult tendons was a narrow layer of fibrocartilage at the junction with the bone (fig. 6). The thickness of this layer varied in different cadavers and in different portions of a single insertion. The width ranged between 1 mm. and a few microns. Fibrocartilage was present in all. The places examined, of course, did not include all portions of the skeleton or all tendinous insertions. The study demonstrated that fibrocartilage is distributed as a normal tissue constituent in places where traumatic ossification occurs.

COMMENT

The abundance of fibrocartilage or cartilage in callus tissue during the early stages of traumatic ossification and the small amount or the absence of these components in fully organized tissue in the late stage suggest that the cartilage matrix is a transition into bone rather than that cartilage develops from the bone. Stages of development from cellular fibrocartilage or hyaline cartilage into trabeculae of poorly differentiated bone and trabeculae of lamellar bone with residues of a cartilage matrix occur regularly in incompletely differentiated callus tissue. Such arrangements imply that the bone trabeculae develop through a process of endochondral ossification. The fibrocartilage which is a normal constituent of many tendon insertions is probably the matrix from which traumatic ossification develops. It is reasonable that a reactive or reparative growth of these tissues provoked by an injury results in the disturbance known as traumatic ossification or myositis ossificans. Evidence that these cartilaginous stages occur in the ossification of tissues near but perhaps not directly continuous with bones is found in case 11.

Endochondral genesis is accepted as a natural process in the development of bone. Accordingly, recourse to the theory of metaplasia of

connective tissue, with its implications, as an explanation of bone formation is unnecessary when fibrocartilage tissues with potentials of bone production have proliferated.

SUMMARY

In the early stages the lesion of traumatic ossification contains large amounts of fibrocartilage or hyaline cartilage continuous into bone with varying degrees of differentiation. Some portions seem to be ossifying cartilage; others have lamellar trabeculae containing residues of cartilage. In the late stages of the lesion there are a high content of lamellar bone and only small traces of cartilage. These conditions imply the origin of bone in a cartilage matrix, that is, endochondral bone formation.

Fibrocartilage is a normal constituent of the insertions of many tendons in which traumatic ossification occurs. A reactive or reparative growth of these tissues initiated by trauma provides a simple explanation for the lesion of traumatic ossification.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Surgical Technic.—Fagerstrom [1] stated that nephroureterectomy is an operation that should be reserved for certain uncommon types of pathologic conditions. Its indication, while at times precise, can be determined only by a thorough preliminary examination of the patient, including the making of proper ureterograms.

The indication for nephroureterectomy in cases of papillary tumors of the renal pelvis is today unquestioned. In other types of pathologic lesions the indication hinges mainly on the size and hydrodynamics of the ureter. When grossly infected kidneys are removed, it is unwise to leave behind a large, nondraining ureteral pouch.

The difficulties of total ureterectomy are not prohibitive, and when combined with nephrectomy the additional time involved is usually inconsequential. The patient presenting average surgical risk withstands the combined procedure with no greater shock than that attending simple

1. Fagerstrom, D. P.: Ureterectomy: Its Indications as an Adjunct to Nephrectomy, J. Urol. **41**:137-150 (Feb.) 1939.

nephrectomy. Secondary ureterectomy is usually performed after months of ill health have debilitated the patient, and the technical problems encountered may be difficult in the extreme. When employed with proper selection, total primary ureterectomy will often circumvent many of the pitfalls of misguided conservative surgical treatment.

Nephrostomy.—Nephrostomy is a conservative operation for temporary or permanent drainage of the kidney; it will preserve renal function or provide an avenue of escape for retained products of infection in the presence of ureteral occlusion. Obstruction of the kidney and the factors affecting its recoverability have been considered.

Graves and Buddington [2] discussed the following indications for nephrostomy as encountered in their series of cases: drainage of the kidney following removal of stones through its cortex; drainage of the kidney during healing of the lines of suture following plastic operations on the renal pelvis or upper portion of the ureter; ureteral occlusion by malignant disease; acute ureteral occlusion by edema following electrocoagulation or irradiation in cases of tumor of the urinary bladder; bilateral nephrolithiasis with marked impairment of the total renal function; as the first step in a two stage nephrectomy; bilateral hydronephrosis, usually congenital in origin, and often associated with atony of the ureter above and below the point of stenosis, with marked impairment of the total renal values; obstruction of the ureter by impassable inflammatory stricture; in association with ureterointestinal anastomosis; as a life-saving measure in cases of profound toxemia arising from severe pyelitis of pregnancy in which milder measures have failed.

Anomalies.—Braasch and Hammer [3] stated that the clinical recognition of renal fusion has become more frequent in recent years as a result of the routine use of excretory urography. Clinical recognition by this method was possible in 95.5 per cent of 102 cases reviewed.

The position of the renal pelves in cases of bilateral fusion is variable, but the following features are of interest: (1) the low situation of one or both renal pelves in relation to the vertebrae—more than 60 per cent being below the third lumbar vertebra—and (2) the closer proximity of the right pelvis to the vertebral margin when the right and the left pelvis are compared. Although in the presence of renal fusion the two pelves usually are situated closer together than normally, the distance separating them is not uniform, and it may be so great that the presence of fusion would seem impossible.

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2. Graves, R. C., and Buddington, W. T.: Nephrostomy: Indications and Technique, J. Urol. **41**:265-281 (March) 1939.

3. Braasch, W. F., and Hammer, H. J.: Renal Fusion: Urographic Data and Their Clinical Significance, Tr. Am. A. Genito-Urin. Surgeons **31**:321-332, 1938.

In differential diagnosis, which may be difficult, the possibility of the presence of the following conditions should be eliminated: (1) bilateral renal fusion and incomplete renal rotation with ectopia and (2) unilateral renal fusion and crossed renal dystopia without fusion.

Evidence of dilatation of either the calices or the pelves, or both, is associated in many cases with renal fusion. This condition usually indicates the presence of stasis. Pyelectasis and caliectasis are sometimes observed in patients who have never had pain. Lumbar pain is sometimes observed in patients who do not have evidence of pyelectasis or caliectasis. Fused kidneys removed at necropsy may show gross evidence of a minor degree of pyelectasis without apparent ureteral obstruction. In some cases, this may be a residual deformity caused by previous obstruction. The existence of renal stasis can best be demonstrated by the use of delayed retrograde urography, and renal stasis will be found present to a variable degree in many cases of renal fusion. It may be a variable factor in indicating the cause of obscure lumbar or abdominal pain.

Soloway [4] stated that bilateral metanephric agenesia is a rare anomaly, and is a condition incompatible with extrauterine life. The infant is frequently alive at birth, but death occurs in a few hours. This condition is usually associated with other equally serious defects of development. In a thorough review of the literature, Amolsch reported 119 cases, including 4 of his own. Twelve cases of renal anomalies observed at postmortem examination were reported. Two more cases of bilateral renal agenesia were reported by Soloway, making the total number of cases reported 121. Bilateral renal agenesia is observed in about 1 of 6,000 necropsies. Soloway also recorded 10 cases of congenital solitary kidney. Of these, the kidney, ureter and ureteral orifice were absent in 8; rudimentary ureters were present in 2; associated genital anomalies were observed in 3, and the adrenal gland was absent in 2 and not recorded in 8. Bilateral renal agenesia is usually found at necropsy, but unilateral renal agenesia is diagnosed more frequently, and proper treatment instituted much earlier than previously, as the result of improved diagnostic methods and more general employment of intravenous urography.

Shoemaker and Braasch [5] stated that the ratio of cases of fused kidney as observed at necropsy at the Mayo Clinic was 1:385. All age groups were well represented in this series of cases. In 24 cases the ureters, pelves and calices were normal except for their position in relation to

4. Soloway, H. M.: Bilateral and Unilateral Renal Agenesis, Ann. Surg. **109**:267-273 (Feb.) 1939.

5. Shoemaker, R., and Braasch, W. F.: Fused Kidney: A Description of the Gross Pathologic Changes in Thirty-Five Cases, J. Urol. **41**:1-7 (Jan.) 1939.

the renal parenchyma. In 11 cases there was some degree of dilatation of the ureters, pelves or calices. In 5 of these 11 cases the dilatation was limited to the calices and pelvis and could be considered the result of the anomaly. The cause of the obstruction in the upper third of the ureter could not be definitely ascertained in a sixth case. There were 8 cases of hypertrophy of the prostate gland and 1 of stricture of the urethra in the total of 35 cases. In 6 of these cases there also was some dilatation of the upper part of the urinary tract, and in 4 of the 6 cases the dilatation was probably secondary to the obstructing lesion in the lower part of the urinary tract. Dilatation was secondary to a vesicocolonic fistula in another case. In 2 of the 35 cases the possibility of fused kidney was suggested by pyelographic examination, but in another case the diagnosis could not be made by this means. Sections were examined microscopically in 21 cases. Fourteen specimens were not available for section. Ten of these specimens appeared grossly normal. Coexistent congenital anomalies were present in 11 cases.

Calculi.—Howze [6] reported 4 cases of large and multiple renal calculi in children. Chronic pyuria is the predominating symptom of large calculi in children. The occurrence of renal calculi in one kidney with coexisting pathologic lesions of the second kidney makes conservative surgical treatment imperative in many cases. The possibility of the dissolution of cystine calculi by medical means demands a more careful study of the urine for cystine crystals in all cases of children having urinary stones. Surgical treatment of the urinary tract is well tolerated by children, and gratifying results frequently can be obtained in cases of badly damaged kidneys.

Hellström [7] said that most urinary infections probably can contribute in some way or another to the formation and development of concrements, but that infection by staphylococci stands alone in this respect, since it is the most common cause of so-called infection stones and since it produces a uniform type of concrement.

Hellström's conclusions were drawn from 100 cases of what he called "primary staphylococcus stones of the kidney and ureter." All calculi with any etiologic factor other than a staphylococcic infection were excluded.

Analysis of 750 cases of renal and ureteral calculi at the Maria Hospital, Stockholm, showed oxalate stones in 63 per cent of the cases, infection stones in 22 per cent and uric acid and phosphate (aseptic) stones, stones of uncertain composition and cystine stones in 5 per

6. Howze, C. P.: Large and Multiple Renal Calculi in Children, Tr. Am. A. Genito-Urin. Surgeons **31**:1-20, 1938.

7. Hellström, J.: The Significance of Staphylococci in the Development and Treatment of Renal and Ureteral Stones, Brit. J. Urol. **10**:348-372 (Dec.) 1938.

cent, each. Seventy-five per cent of the "infection stones" were caused by staphylococci; of these, 57 occurred in men and 43 in women. Ninety-six per cent of the patients were between the ages of 20 and 50. Thirty per cent of the stones were bilateral, a higher percentage than is generally found for aseptic stones because staphylococcuria is often bilateral. Likewise, multiplicity is more frequent in the infectious than in the aseptic type.

Of the 100 patients observed, 74 had renal stones and 45 had ureteral stones. Analysis of the stones in this series showed all of them to be composed of amorphous phosphates, triple phosphates and calcium carbonate, in varying proportions.

The organic substance of the stones was largely composed of staphylococci, and after decalcification and staining, these organisms were seen lying in concentric layers in an amorphous fibrillar substance.

Patients having these stones generally give a history of a long-standing, low grade urinary infection with recurrent attacks of cystitis or pyelitis. There is often a whitish, sandy admixture in the urine near the completion of micturition, and there is chronic staphylococcuria. Because these organisms split urea, the urine rapidly becomes alkaline if it stands. Despite the fact that staphylococci appear in masses in the sediment, they grow poorly in the common nutrient culture mediums, so that staining the fresh specimen is of great importance.

Hellström said that every patient having staphylococcuria should have a careful roentgenologic examination, including a ureteropyelogram. Cystoscopy often shows few cystitic changes, and the marked ulceration and incrustation which Rovsing stated were characteristic of urinary infections with urea-splitting organisms were not observed in Hellström's cases. Likewise, there was little parenchymal suppuration in the kidneys. The chief condition was pyelitis and ureteritis with round cell infiltration in the submucosa, most pronounced in the niches of the calices. Hellström said that formation of stone often begins there.

Treatment of the staphylococcic infection is not effective unless the stones have been removed or are passed at micturition.

General measures consist of acidification of the urine by means of the acid ash diet and calcium or ammonium chloride. Although Hellström found no evidence in his large series of cases of urinary stones that avitaminosis was an etiologic factor, he prescribed administration of vitamin A postoperatively.

Vaccines and bacteriophage are of little value. Sulfanilamide can be used, but the best preparation is neoarsphenamine, in doses of 0.15 to 0.3 Gm. every three or four days. Administration of acetarsone by mouth is of value. Lavage of the renal pelvis with a mixture of solu-

tion of boric acid and potassium permanganate (1:4,000) has been useful. Hellström said that this mixture is the best of the preparations commonly used for this purpose.

Conservative treatment, consisting of expectant therapy, ureteral catheterization and pelvic irrigation, was employed for 20 of his patients, resulting in cures for 18.

Of the 80 patients operated on, 31 had ureterolithotomy, 28 pyelolithotomy, 25 nephrectomy, 21 nephrolithotomy, 2 renal resection, 1 ureterostomy, 3 decapsulation and nephrostomy and 2 suprapubic cystostomy, plus snipping of the ureteral orifice. There was 1 death, a mortality rate of 1.25 per cent.

The late results were as follows:

	No. of Cases
No stones; sterile urine	26
No stones; bacilli	7
No stones; staphylococci	3
Stones still present; no new ones	8
Recurrence on the side of operation, probably arising from remaining stones	5
Recurrence on the side of operation from new formation of stones	11
Recurrence on the other side by new formation	6
Recurrence on both sides by new formation	8
Results uncertain	5

Recurrences probably arising from remaining stones were observed in 5 cases, and genuine recurrences arising from new formation of stones were observed in not less than 25 cases. The genuine recurrences appeared on both sides in 8 cases, on the side of operation only in 11 cases and on the opposite side only in 6 cases. Thus, altogether, 19 patients had genuine recurrences on the side of operation; 6 of these patients had undergone pyelolithotomy, 5 nephrolithotomy and 8 ureterolithotomy. Nearly half the recurrences appeared within the first year after operation, and 2 within only one month after operation. If the patients with stone bilaterally are included, recurrences were observed on the side opposite that of operation in 14 patients, 3 of whom had undergone pyelolithotomy, 2 nephrolithotomy, 4 ureterolithotomy, 1 suprapubic cystotomy and papillolithotomy and 4 nephrectomy. Generally, the recurrences took a longer time to appear on the intact side than on the side of operation.

The most important cause of recurrence is persistent or recurrent staphylococcic infection. The fact that most recurrences occurred after ureterolithotomy is evidence against the importance of operative trauma, for in the presence of aseptic stones ureterolithotomy is the operation least likely to be followed by recurrence.

Of the patients having recurrent stones, 12 later underwent one or more operations for the condition, and in 15 instances spontaneous passage occurred. This resulted in 18 of the patients with recurrent stones becoming free from stones, and of these, 8 have also become free from bacteria. Of all the patients operated on—primarily or for recurrence—only 34 (42.5 per cent) have been freed from calculi and bacteria. The prognosis in operations for staphylococcic stones is thus rather poor so far as complete cure is concerned.

Measures to improve these results consist in taking roentgenograms at the time of operation, lavage of the renal pelvis after it has been opened, drainage of the stoma created by nephrostomy, correction of obstruction by nephropexy, ureterolysis, plastic surgical treatment of the renal pelvis or renal resection, and initiation of measures to control the infection after operation. Nephrectomy may be the most conservative operation at times. In Hellström's series, recurrences were present in the remaining kidney after nephrectomy in only 1 instance (4 per cent), while after conservative measures had been instituted recurrences were present on this side in 20 per cent of cases.

Smith [8] stated that renal infection is not a factor of major importance in the formation of the majority of primary renal calculi. In the formation of recurrent stones, except those caused by hyperparathyroidism and cystinuria, infection is of the greatest importance. In such cases Bacillus proteus is the organism most commonly observed. The urologist's duty is not fulfilled by removal of the stone; he must then employ every known measure to eradicate the renal infection. In order to do this successfully, he must vary his surgical procedure according to the circumstances in the case. This may mean performance of nephrectomy, partial nephrectomy, nephrostomy or pyelotomy. In no instance of renal stone should the outcome be regarded as satisfactory until the urine of the patient has become sterile.

Jáki [9] discussed the formation of renal calculi in cases in which vitamin A is lacking. He stated that avitaminosis in rats causes stones in a large percentage of cases. The urine of these animals is alkaline and infected, and the stones are usually phosphatic. Avitaminosis rarely occurs in man, because vitamin A is found frequently in the common foodstuffs. On the other hand, in fully 90 per cent of cases renal stones are unilateral. Jáki offered these two facts to refute the statement that stones in man are frequently associated with lack of vitamin A. He further stated that with the exception of Higgins, no investigator had been able to prove that avitaminosis or hypovitaminosis

8. Smith, G. G.: Renal Infection and Nephrolithiasis, Surg., Gynec. & Obst. **68**:527-533 (Feb. 15) 1939.

9. Jáki, J.: Das Vitamin A und die Harnsteinbildung, Ztschr. f. Urol. **32**: 750-756 (Nov.) 1938.

was the cause of formation of stone in his patients. In the advanced stage there is a decrease in the concentration of vitamin A in the blood and tissues. Stones are more common in young persons, who have larger amounts of vitamin A than others. Jáki concluded that the administration of vitamin A may aid in the prevention of recurrence of stones, but that it should be used only as an adjunct to other means of prevention of the formation or recurrence of stone.

Harbitz [10] stated that after appendectomy pathologic constituents in the urine are not infrequently found, and that in about 1 per cent of the cases hematuria is macroscopically visible. Hematuria usually appears in the course of the first eight days after operation, and is encountered especially in children—in Harbitz' experience, chiefly in little girls. The nature of the hematuria has not been ascertained, but it must be supposed to be caused by hemorrhagic nephritis. Often Bacillus coli is found in the urine at the time of hemorrhage. In cultural experiments, however, it has not been possible to obtain a growth of bacilli which might be the cause of the renal disturbance and the hemorrhage.

The hematuria is in general not attended by important symptoms, but all degrees of hematuria have been found, up to serious acute hemorrhagic nephritis, which may end in complete anuria.

The prognosis seems to be good in all cases. Even patients having anuria progressed to good health, and the illness seemed to have been cured.

In a few cases the postoperative hematuria may be due to formation of concretions in the urinary tract soon after appendectomy. In other cases it is seen that urinary concretions are formed a long time after the appearance of postoperative hematuria, and these stones cause attacks of pain and renewed hematuria. Such formation of calculi was, in Harbitz' material, seen in 3 children. This is unusual, since formation of concretions in childhood is otherwise of rare occurrence in Norway.

Tumors.—Cabot and Middleton [11] stated that renal adenomas occur most frequently in the years of greatest incidence of degenerative vascular disease. There is no conclusive evidence to contest the repeated assertion that adenomas are usually formed as a result of occlusion and dilatation of renal tubules.

The cystic spaces commonly seen in papillary adenomas probably represent, in most cases, the stage of development preceding the forma-

10. Harbitz, H. F.: Haematuria and Renal Calculus as Complication After Appendectomy, Acta chir. Scandinav. **81**:405-424 (Jan. 13) 1939.

11. Cabot, H., and Middleton, A. W.: The Relation of So-Called Adenoma of the Kidney to Carcinoma of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **31**:91-105, 1938.

tion of the multiple papillary projections that compose this tumor. However, the presence of calcium and other evidences of chronicity in some instances suggests that cysts may also occur as a result of degeneration of an adenoma. One microscopic section suggested that adenomas may occur in association with polycystic disease.

The renal adenoma is not a transitional stage between tissue of benign character and tumors of known malignancy, as is commonly stated, but is itself a malignant growth.

Bugbee [12] stated that a malignant condition of the urinary tract, whether located in the kidney, bladder or prostate gland, can be cured only by complete removal while the lesion is still localized. This procedure can be effected only on the basis of an early diagnosis, which may be difficult because of the late appearance of physical signs and symptoms suggesting the presence of a malignant growth.

Nephrectomy, carried out under satisfactory exposure and with as little traumatism as possible, will result in a certain number of cures.

Tumors of the bladder, although easily diagnosed, are often allowed to become extensive before being discovered. Fulguration and transurethral resection produce excellent results in cases of low grade papillomas and in certain instances of papillary carcinoma, whereas infiltrating carcinoma is often radioresistant and the only surgical treatment applicable may be total cystectomy following deviation of the urinary stream.

Cancer of the prostate gland is essentially a fatal disease. Rarely is complete removal of the lesion possible. As a rule, by the time the diagnosis has been made the disease has extended beyond the capsule, and the surgeon's efforts may best be expended in restoring urinary function, a procedure which may be accomplished with a minimum of risk to the patient by means of transurethral resection. It should be borne in mind that most cancers of the prostate are of slow growth.

The watchword should be "early diagnosis," with constant emphasis on the necessity of ascertaining the origin of erythrocytes found in the urine, for only through such means will the surgeon be able, in the light of present knowledge, to substitute methods of cure for palliative treatment in the management of malignant genitourinary tumors.

Barney and Churchill [13] stated that adenocarcinoma of the kidney (hypernephroma) may on occasion be treated by removal of the primary growth and that this tumor apparently has but a single metastasis. They reported the case of a patient in whom roentgenologic evidence of a metastatic nodule in the lung was the first sign of disease. Nephrectomy

12. Bugbee, H. G.: Surgery of Genito-Urinary Malignant Tumors, J. A. M. A. **112**:298-301 (Jan. 28) 1939.

13. Barney, J. D., and Churchill, E. D.: Adenocarcinoma of the Kidney with Metastasis to the Lung, Cured by Nephrectomy and Lobectomy, Tr. Am. A. Genito-Urin. Surgeons **31**:71-79, 1938.

was performed five months later, and fifteen months after nephrectomy the pulmonary metastasis was excised by subtotal lobectomy. The patient was alive five years later and in good health, without evidence of disease. Barney and Churchill stated that metastases to the lung occur not infrequently as the result of adenocarcinoma of the kidney. There is clinical and roentgenologic evidence that these metastases may occasionally undergo spontaneous regression.

Hemorrhagic Cysts.—Scholl [14] reported a case of hemorrhagic cyst of the kidney in a man 58 years of age, who had had a swelling of the abdomen for three years. A tumor was found in the region of the left kidney; the tumor spread from the left costal margin to the lower part of the right flank, almost completely filling the left side of the abdomen and extending into the right side. The patient had undergone prostatectomy six years previously, at which time he had pain in the region of the left kidney. Roentgenograms of the abdomen disclosed a large, rounded tumor of soft tissue, filling the left side and extending across the midline into the right side. Peritoneoscopy disclosed that the left lobe of the liver was pushed to the right and that the stomach was displaced upward by a large tumor, which occupied three fourths of the abdominal cavity. Cystoscopic and pyelographic examination showed moderate dilatation of the pelvis, in the upper region of the tumor. It was thought that the kidney was separate from, and not involved in, the structure of the tumor.

The tumor was explored surgically through a straight left rectus incision, with the patient under gas anesthesia. The colon was pulled toward the midline, and an opening was made in the mesocolon of the descending colon and the upper portion of the sigmoid flexure. The left kidney was large, and on both poles and projecting from its under surface were several large cystic dilatations, which extended from the diaphragm to the pelvis and across to the lower right abdominal quadrant. The entire cystic mass was gently dissected out, most of it by blunt, but some by sharp, dissection. Because of firm adhesions, it was impossible to remove the mass intact. When it was torn, a large amount of old, chocolate-colored clots and black fluid escaped from the cystic mass. The patient readily recovered after the operation.

The specimen removed consisted of the enlarged kidney and an extremely dilated sac. The capsule of the kidney was continuous over the wall of the cyst, the wall varying from 3 to 6 mm. in thickness. There was no evidence of involvement of renal parenchyma in the wall of the cyst, such as is usually seen in cases of hemorrhagic cyst. The inner layer of the wall was composed of old hemorrhagic masses of

14. Scholl, A. J.: Hemorrhagic Cysts of the Kidney, J. Urol. **41**:103-110 (Feb.) 1939.

organized clots and fibrin. Some of the clots were extremely adherent to the wall of the cyst and could be removed only by tearing. The cyst, which on external examination appeared to be multilobular, was solitary and was filled with organized and partly organized blood clots, together with a large amount of thin black fluid. Some of the clotted masses were apparently old, since they contained shreds of fibrin and were hard and difficult to tear apart. At the base of the cyst there was a tumor about 8 cm. in diameter, which had spread through the renal capsule to infiltrate the tissues around the ureter and renal vessels. Histologically, this tumor was a rapidly growing papillary adenocarcinoma of the clear cell type.

Tuberculosis.—Wildbolz and Walthard [15] stated that it is generally admitted that the early foci of renal tuberculosis are found in the papillae. Tuberculous changes in the renal cortex seem to be either secondary or the result of miliary tuberculosis. Wildbolz and Walthard speculated on the possibility that these changes in the cortex may in some cases be the primary lesion.

Medlar's studies led him to believe that this may often be the case. The kidneys he examined were those taken from patients who had died of tuberculosis, but whose urinary tracts had not been examined before death; consequently, Medlar's results are not above criticism.

Wildbolz and Walthard described a case which definitely proved that chronic renal tuberculosis may start in the cortex. Acid-fast bacilli were found in the urine from the right kidney of a girl of 19 years. Long search revealed nine small foci in the renal cortex, and none elsewhere.

Clairmont and Schaffhauser [16] stated that in their experience with a large number of cases of congenital tuberculosis they have found that the average urologist has not had sufficient training or experience to give them (the authors) the necessary information regarding the diagnosis and therapeutic progress. They further stated that even the slightest abnormal observation as to the condition of the urine should be investigated until the reason for its appearance is clear. If tubercle bacilli are found in the urine, a complete urologic examination must be made to find the focus of tuberculosis. A thorough investigation often leads to the correct diagnosis and proper treatment of the condition. The increasing interest of physicians in sanatoriums in this problem suggests that many questions which are now unanswered may be solved in the future.

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15. Wildbolz, H., and Walthard, B.: Die primär corticale, nicht verkäsende chronische Nierentuberkulose, Ztschr. f. urol. Chir. u. Gynäk. **45**:1-15, 1939.

16. Clairmont, P., and Schaffhauser, F.: Die Nierentuberkulose, Zentralbl. f. Chir. **65**:1115-1135 (May 7) 1938.

Clairmont and Schaffhauser, in their clinic in Zurich, Switzerland, have, for many years, laid great stress on the value of early diagnosis of renal tuberculosis in the teaching of students and doctors of medicine. The average physician shows a tendency to treat chronic cystitis too long without making a proper diagnosis. Clairmont and Schaffhauser distinguished between acute or subacute miliary and the chronic forms of renal tuberculosis. There are three types of chronic renal tuberculosis, as defined by Wildbolz—the caseocavernous, the nodular and the fibrous. In 11 cases of early tuberculosis the authors found the focus in or around the renal papillae. Papillary tuberculosis, described by early authors, is the typical initial form of chronic caseous tuberculosis. Clairmont and Schaffhauser, concluded that stenosis is significant when it occurs at the ureteropelvic juncture, as a result of tuberculous ulcers with only a papillary focus. Conditions of this type lead early to severe infection of the pelvis of the kidney. Patients having primary tuberculosis of the pelvis of the kidney without foci of tuberculosis in the parenchyma should be observed with care. In 2 of the authors' cases a small primary focus was observed in a renal pyramid only after a thorough anatomic examination of the kidney. Infections in the papillae may remain isolated, or originally open foci may become excluded from the pelvis, resulting in clinical healing after pyuria and tubercle bacilli in the urine have disappeared. The authors have observed 3 such instances. Conditions of this type may mistakenly be considered as tuberculous bacilluria or as spontaneous healing of renal tuberculosis. Control over a long period shows that these foci as a rule recur and result in progressive urogenital tuberculosis.

Autonephrectomy may result from extensive fibrous healing and formation of scar tissue. Numerous observations have shown that renal lesions of this kind may easily initiate general tuberculosis. It is urgently advised that such kidneys be removed, even though the patient exhibits no symptoms. Spontaneous recovery of patients having caseous tuberculosis, with complete control, has been described only twice in the literature—once by Castaigne and once by Wildbolz. Medlar's studies do not necessarily prove that healing of this type of chronic tuberculosis can occur. His work was done on kidneys involved by a miliary form of tuberculosis, and not by early caseocavernous infections, which were discussed by Clairmont and Schaffhauser. It is possible that tuberculous nephritis, a noncaseous, rarely occurring form of renal tuberculosis, may eventually heal. A differential diagnosis of tuberculous nephritis and early caseous tuberculosis may be impossbile to make for many years. Wildbolz has seen 20 cases of this type in more than 1,300 observations, and only 4 of the patients concerned showed clinical recovery which was controlled over a period of many years.

The question of tuberculous bacilluria has not been definitely settled. Clairmont and Schaffhauser expressed the belief that it does not exist. The finding of tubercle bacilli in urine which has been taken directly from the kidney under proper precautions must be controlled over a period of years. Only long-continued observations may prevent errors. The authors observed a patient more than five years; the patient seemed to show spontaneous recovery, but bilateral caseous renal tuberculosis later developed. Nephrectomy is indicated only when the other kidney is healthy and when the diseased kidney exhibits marked pyuria and decreasing function. In considering the symptomatology of renal tuberculosis, Clairmont and Schaffhauser emphasized so-called amicrobic pyuria, which has nothing to do with tuberculosis. Statistics show that most patients having unilateral renal tuberculosis who are treated conservatively die within the first five or six years. In contrast to this are the favorable results of nephrectomy, which constitute satisfactory cures in 80 per cent of the early cases and in 50 to 60 per cent of the late cases. Early diagnosis is desirable, and early nephrectomy is the treatment of choice in cases of unilateral renal tuberculosis.

Hydronephrosis.—Jewett [17] stated that accessory renal vessels at the lower pole of the kidney are frequently associated with obstruction in the region of the ureteropelvic junction. In some of these cases the underlying cause is stricture, which is probably a primary pathologic entity.

In certain cases of hydronephrosis, accessory renal vessels are the chief cause of the obstruction, which is precipitated, usually in early adult life, by the effect of one or more subsidiary factors, of which the mechanism of renal growth is possibly one of the most important. Surgical intervention designed to eliminate obstructive contact is indicated. Success depends largely on the severity of infection and the extent of cortical destruction.

Odén [18] reported a case of ectopic kidney. The patient, a man, had been operated on more than forty years previously because of repeated abdominal pains and a palpable cystic swelling in the lower part of the abdomen, congenital double urinary bladder being regarded as the condition responsible. At this operation a communication had been established between the two "urinary bladders." After freedom from symptoms for forty years, the patient had had pains in the left part of the abdomen. These pains had extended partly upward toward the region of the kidney and partly downward, and were associated

17. Jewett, H. J.: Accessory Renal Vessels: Their Influence in Certain Cases of Hydronephrosis, Surg., Gynec. & Obst. **68**:666-676 (March) 1939.

18. Odén, O.: Ein Fall von Ectopia renis mit Hydronephrose und karzinomatöser Degeneration, Acta chir. Scandinav. **81**:425-438 (Jan. 13) 1939.

with frequency of micturition and occasional hematuria. On examination and surgical exploration of the left renal pelvis, a floating kidney was observed in the small pelvis, with hydronephrosis. Since the patient was having pain, the kidney was removed. On microscopic examination, the wall of the renal pelvis proved to be the seat of cancer. The parenchyma of the kidney was completely atrophic. From the communication between the hydronephrotic sac and the bladder that had been established by the operation forty years earlier, there still remained an exceedingly narrow canal. The recent symptoms which brought the patient to the physician had in all probability been caused by the subsequently detected cancer.

Notwithstanding the many brilliant results obtained with plastic procedures for the repair of hydronephrosis, the opposition to them has not subsided. Wildbolz,[19] therefore, published the results obtained in the treatment of a series of patients operated on by Quinby and reexamined ten or more years after operation. Six patients had excellent function of the repaired kidney and marked improvement in the shape of the renal pelvis ten to twenty years after operation. In only 1 case had the treatment failed; the patient was found to have continuation of the hydronephrosis, with further decrease in renal function.

Parenchymal Infection.—Jeck [20] stated that large solitary abscess of the renal parenchyma is not often seen and that it is less often recognized preoperatively. He reported 2 cases of solitary renal abscess.

In most of the reported cases in which cultures were made of the pus evacuated from the cavity of the abscess, Staphylococcus aureus was obtained in pure culture. Many of the patients reported on gave a history of a preexisting lesion, such as a boil or other type of staphylococcic infection of the skin.

A history of boils, carbuncles, paronychia, acute osteomyelitis, infected teeth, tonsils or similar foci of infection is of the utmost importance in establishing a diagnosis when other signs point to the kidney. In all types of such infections the physician usually observes chills to be followed by the "spiking" type of increased temperature, pain in the loin on the affected side, a moderately high leukocyte count, a low erythrocyte count with a low percentage of hemoglobin and, finally, rather marked loss in weight.

The urinary findings are often not pertinent, and are therefore frequently misleading. The urine may contain a few leukocytes or staphylococci or both, but at times does not contain either. In many

19. Wildbolz, E.: Enderfolge organerhaltender Operationen bei Hydronephrose, Ztschr. f. urol. Chir. u. Gynäk. **45**:31-39, 1939.

20. Jeck, H. S.: Large Solitary Abscess of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **31**:21-28, 1938.

instances, functional tests of the kidney show little or no difference in the functioning capacity of the two kidneys.

The treatment of large solitary abscess of the kidney is incision and drainage. On exposure of the kidney in the presence of suspected abscess, if the abscess is not at once apparent, decapsulation of the kidneys should be performed, for a solitary abscess or multiple abscesses may not be discovered until the true capsule of the kidney is removed.

The 66 cases of renal carbuncle reviewed by Graves and Parkins, together with the 36 cases reviewed by Spence and Johnston,[21] make a total of 102 cases reported to date.

In the 36 cases reported by Spence and Johnston, there were 20 males and 16 females. The average age was 32, the youngest patient being 9 and the oldest 65. The right side was involved in 19 instances, the left in 16; 1 patient had bilateral involvement. All but 1 patient had pain on the involved side; 36 per cent had chills, and 60 per cent had fever. Unexplained weakness, malaise, loss of weight and strength, while variable, were often present. History or evidence of a primary focus of infection was elicited in 78 per cent of cases and was absent in 22 per cent.

In every instance in which the records were complete, there was tenderness, graded from slight to marked, over the involved side.

Results of analysis of urine from the bladder were essentially negative in 25 of the 36 cases. The average leukocyte count was 17,400 in the 20 cases in which it was recorded; the maximal count was 28,600, the minimal, 9,400. In only 2 cases was it less than 10,000. Results of culture or examination of a smear of pus obtained from the carbuncle at operation were recorded in 28 cases. In 27 of these, some strain of Staphylococcus either was present in pure culture or predominated.

Of the 23 cystoscopic examinations made, the results of 13 were without significance, and 10 disclosed pus or bacteria in the renal specimen. Renal function was normal on the affected side in 14 cases, diminished in 7 and not recorded in 15.

In regard to the roentgenographic data, the series of Spence and Johnston differed markedly from that of Graves and Parkins. In 66 cases in the latter series there were only 15 abnormal pyelograms, while in 36 cases in the series of Spence and Johnston, 22 pyelograms were abnormal and in only 4 instances were normal pyelograms obtained.

The treatment of patients having this condition is surgical. On reviewing the results of treatment in this series, the distinct impression is gained that as a general rule, unless more than a third of the kidney

21. Spence, H. M., and Johnston, L. W.: Renal Carbuncle: Case Report and Comparative Review, Ann. Surg. **109**:99-108 (Jan.) 1939.

is involved, conservative procedure is preferable as the first step, and is more often than not sufficient.

Thirty-five patients were operated on in Spence and Johnston's group of 36, the exception being a patient dying of cerebral abscess, on whom necropsy was performed. Primary nephrectomy was carried out in 17 cases, with 1 death, possibly resulting from disseminated miliary tuberculosis three months after operation. Incision and drainage of the carbuncle were performed in 9 instances, with no fatalities. Partial or complete excision or enucleation of the lesion was performed in 6 instances, with 1 death resulting from lobar pneumonia. In 1 of these cases nephrostomy was performed when a calix was broken into. Two patients had drainage of a perinephric abscess without recognition by the surgeon of the presence of a carbuncle; the patients failed to improve, and later secondary nephrectomy was performed. In 1 case the carbuncle was treated by electrocoagulation, but the patient later required nephrectomy. In all, 52 per cent of the patients were originally treated by conservative surgical operation.

Hypertension.—Crabtree [22] discussed cases of unilateral infection of the urinary tract in which the patients either were cured of their hypertension or were markedly benefited by removal of the infected kidney. These cases are of particular interest, because they do not represent terminal conditions; the specimens removed for study were pathologic specimens obtained at operation and not specimens taken at necropsy, with terminal alterations. The fate of the other kidney will in some, if not in all, instances be determined eventually.

Crabtree collected 5 cases of unilateral destructive renal lesions associated with hypertension in which the patients improved after nephrectomy, and he added a sixth case.

Crabtree stated that from a survey of the data pertaining to this group of cases it may be concluded that the term "cure" after operation should be used with reservations. Whereas in 3 cases the data seem to indicate complete recovery for periods as long as two, fifteen and twenty months, respectively, in the other cases return of hypertension is known to have occurred in two months, and there is no certainty about the freedom of the remaining kidney from permanent damage at the time the operation was performed.

Crabtree concluded that there is a small group of cases in which patients are both children and adults and in which hypertension associated with unilateral renal disease either retrogresses so far as the patient has been followed or is greatly, although temporarily, relieved by nephrec-

22. Crabtree, E. G.: Hypertension in Destructive Infected Unilateral Lesions of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **31**:299-319, 1938.

tomy. The constant observations in these cases are obstruction to the outflow of urine and damage to the renal parenchyma, which in all cases is extensive and hypoplastic in type, with involvement of the substance of the cortex of the kidney, either in infective processes which are healing or in still active processes with abscesses. In 5 of the six cases reported by Crabtree, bacteria were still present in the infected kidney at operation. No single type of infecting agent was encountered. Both coccic and bacillary types of infection were found.

Striking recessions in blood pressure followed nephrectomy in all 6 cases. The lapse of time was not sufficient in 4 cases to allow speculation as to outcome. The decrease in blood pressure persisted for two months in 2 instances, fifteen months in another case and twenty months in the fourth. In 1 of the cases of two months' duration the concentration of nonprotein nitrogen was elevated; there was an increase in blood pressure, and the concentration of nonprotein nitrogen fluctuated with it. Whereas both the blood pressure and the blood chemistry were normal, the excretion of phenolsulfonphthalein by the remaining kidney was not normal.

"Cure" is not necessarily the proper term to apply to results of treatment of these patients. Whether or not in the end cure is accomplished in any instance, nephrectomy appears to be a good therapeutic measure for prolongation of life of the patient.

Decapsulation.—Linder and Sarre,[23] using Rein's thermostromuhr, examined the renal blood flow in dogs after experimental mercurial poisoning and noted the reaction of the blood flow after renal decapsulation. The renal blood flow was reduced to 40 per cent of its original rate three hours after the intravenous administration of 7 mg. of mercury bichloride per kilogram of body weight. When the kidney was decapsulated at once the blood flow was not reduced, but remained constant. Its decrease was therefore caused by mechanical factors, probably the swelling of the tubular epithelial cells. In consequence, Linder and Sarre recommended early decapsulation.

Nephrobronchial Fistula.—Lee [24] reported 2 cases of nephrobronchial fistula. He stated that nephrobronchial fistula, although it is a rare condition, should be considered when a patient having renal disease or perinephric abscess is afflicted with severe cough which is productive of purulent sputum. Drainage of the perinephric abscess relieves the cough and sputum and cures the pulmonary involvement.

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23. Linder, F., and Sarre, H.: Dekapsulation und Durchblutung der Sublimatniere, Ztschr. f. urol. Chir. u. Gynäk. **45**:40-48, 1939.

24. Lee, H. P.: Nephrobronchial Fistula, with Reports of Two Cases, J. Urol. **41**:117-125 (Feb.) 1939.

Pyelonephritis.—Braasch [25] stated that since pyelonephritis is often secondary to infection in the lower portion of the urinary tract, treatment must be directed to this source in order to prevent recurrence.

Elimination of pus from the urine and cessation of symptoms do not necessarily mean that infection has been completely eliminated. Repeated cultures must be made subsequently to insure recovery.

Recent developments in chemotherapy have provided physicians with two compounds which are much more efficacious in the treatment of infection in the urinary tract than any other drug previously employed, and often produce miraculous results. They are sulfanilamide and mandelic acid. Compounds of sulfanilamide should be used more frequently than at present as a preventive of infection, such as occurs when postoperative retention of urine is present. The bactericidal influence of sulfanilamide in small doses is employed for this purpose, and also in other types of urinary infection.

With the increasing efficacy of chemotherapy and the development of special vaccines, it may be predicted that primary pyelonephritis will be largely limited to the acute and subacute stages of the disease and that chronic pyelonephritis with its complications will develop only occasionally. Adequate treatment of it will, however, entail a thorough study of all the factors involved, including the bacterial, physiologic and anatomic factors.

Adrenal Tumors.—MacKenzie and McEachern [26] described a case of paroxysmal hypertension induced by adrenal pheochromocytoma. A man of 29 had suffered attacks of increasing severity for eighteen months. Attacks lasted three to twelve minutes and were characterized by nausea, substernal distress, generalized and localized headache, tremor, pallor and numbness of the extremities and were followed by exhaustion. During attacks there were a great increase in blood pressure, slowing of the heart rate, disappearance of the radial pulse, decrease in dermal temperature, lymphocytic increase in the blood stream and glycosuria. In the intervals between attacks the blood pressure was normal, and there was no cardiovascular abnormality. Plain roentgenograms, intravenous pyelograms and massage over the adrenal glands failed to demonstrate presence of the tumor. Surgical exploration of the region of the left adrenal gland revealed no tumor. Exploration on the opposite side showed an encapsulated pheochromocytoma, the size of a golf ball (weight, 24 Gm.), which was removed

25. Braasch, W. F.: Pyelonephritis and Its Treatment, Surg., Gynec. & Obst. **68**:534-539 (Feb. 15) 1939.

26. MacKenzie, D. W., and McEachern, D.: Adrenal Pheochromocytoma: The Syndrome of Paroxysmal Hypertension; Report of a Case and Relief by Operation, Tr. Am. A. Genito-Urin. Surgeons **31**:127-154. 1938.

from the adrenal medulla. An extract of it contained a large amount of epinephrine (0.38 Gm. per hundred grams of tumor). No further attacks occurred after operation, and eleven months later the patient reported that he was entirely well.

Data are recorded in 20 cases in which patients were subjected to operation. Five patients died, and 15 were completely relieved. Evidence indicated that the paroxysms of hypertension were due to the intermittent hypersecretion of epinephrine by the adrenal chromaffin tumor.

Cahill [27] stated that what are described as "adrenal cortical syndromes" are more frequently encountered without than with an accompanying demonstrable adrenal tumor. The syndromes are often characterized by sexual changes in the direction of adult masculinity in the female (androtropic), and rarely by feminization of the male (gynecotropic). They are also characterized by more than normally rapid advancement toward maturity in the young (prematurity) or the appearance of more advanced age in the mature (presenility). In some patients there are also present general metabolic changes, more particularly in the plasma, skin and adipose tissue, and in the psychologic status. In some instances one type may predominate; in others all trends may be present.

For diagnosis, visualization of the adrenal glands by the injection of air and roentgenographic examination was used to differentiate between tumorous and nontumorous involvement.

Excretion of androgenic substances in the urine seems to vary with the extent of sexual change and may be present both in patients not having a tumor and in those having a tumor, and may be reduced after removal of the tumor or, if no tumor is present, after diminution of the adrenal cortex. A specific hormonal substance may be excreted in the presence of some tumors.

The operative risk in the surgical treatment of androtropic tumors is less than that accompanying treatment of tumors characterized by marked metabolic changes in the patient, because in the latter instance atrophy of the opposing adrenal gland appears to be frequent. The atrophy may be prevented by preoperative therapy.

Removal of the tumor produces a symptomatic cure, but does not correct the fixed anatomic changes, and hirsutism of the face often persists.

There are apparently temporary sympathetic changes in the menstrual sphere in patients who do not have a tumor, following operative

27. Cahill, G. F.: Adrenal Cortical Syndromes and Adrenal Tumors, Tr. Am. A. Genito-Urin. Surgeons **31**:111-126, 1938.

decrease in the amount of the adrenal cortex. Changes in bodily contour and the mammae have been noted, but none in hirsutism, the genitalia or the voice.

Ureteral Inflammation.—Hager and Boetticher [28] reported a case of membranous inflammation of a ureteral stump with spontaneous rupture. A woman aged 60 had had vesical trouble for many years. The condition had recently become worse, with a sense of painful pressure, dribbling and burning on urination, and at times she had had an incessant desire to urinate. This sensation was often followed by the passage of large pieces of tissue, with considerable relief. The right kidney had been removed twenty-one years previously, and right oophorectomy and appendectomy had also been performed. Results of the general physical examination were essentially normal. Examination of the external genitalia revealed a solid, tenacious, grayish brown tissue protruding from the urethral meatus. This tissue was removed and was found to be an aggregation of elastic-like tissue.

Cystoscopic examination revealed diffuse cystitis. Both meatuses were in normal position. Clear urine in normal spurts was seen issuing from the left ureter. Hanging out of the right ureteral orifice was an irregular white mass, which could be made to float with irrigating fluid. The appearance of this mass was much like that of the tissue that had previously been removed from the urethra. A catheter was passed up the right ureter for a distance of about 10 cm., with drainage of foul-smelling, purulent material; the left ureter was catheterized, without difficulty and with rapid drainage. Through the catheter in the right ureter an opaque medium was injected, which procedure showed a rather marked dilatation of the ureteral stump with inclusion of the original shadows. A diagnosis was made of empyema of the right ureteral stump, with membranous ureteritis.

The patient was readmitted on several occasions with somewhat similar symptoms. At her last entry, because of inability to remove the tenacious material with a cystoscopic rongeur, it was felt that irrigation of the bladder, together with instillation of sterile olive oil, would assist in expulsion of the mass. This was done, and after several days a large mass of tissue, measuring 4 by 3 cm., was passed. Severe pain in the lower right portion of the abdomen developed, together with a sore spot in the back over the region of the scar on the right side. Examination showed an inflamed, indurated portion, about 4 cm. in diameter, in the region of the old surgical scar. With the patient under general anesthesia, about 30 cc. of thick, foul-smelling material

28. Hager, B. H., and Boetticher, E. O.: An Unusual Case of Membranous Inflammation of a Ureteral Stump with Spontaneous Rupture, J. Urol. **41**:151-156 (Feb.) 1939.

was aspirated, culture of which showed the presence of an anaerobic streptococcus. The abscess was then incised and drained, after which the patient became much better.

Most instances of empyema of the ureteral stump are associated with stenosis of the most dependent portion of the structure or with stone. In the case reported, judging from the size of tissue protruding from the ureteral meatus as well as from the ribbon-like coils of material accumulated in the bladder, an impediment to drainage did not seem to be a constant factor. Neither was any difficulty encountered in introducing catheters the length of the residual ureters of this patient.

Dilatation.—In discussing dilatation of the ureters in children, Vermooten [29] emphasized Chwalla's discovery that at about the second month of embryonic life, at the moment the ureter separates from the wolffian duct, its vesical end becomes occluded by an epithelial membrane.

Attention was also directed to Brown's observations that in a mouse embryo metanephric secretion begins on the fifteenth to the sixteenth day, and that hydronephrosis and hydroureter develop, become evident by the seventeenth day and are well marked by the eighteenth day. Further, on the nineteenth to the twenty-fifth day, either the obstruction at the ureterovesical junction spontaneously disappears or hydronephrosis becomes an established fact. These observations on mice apparently confirm those of Chwalla on human embryos.

It was suggested that it is the pressure of the metanephric secretion in causing ischemia of the delicate membrane that is responsible for sloughing of the membrane and in that way permitting the secretion to pass into the bladder.

The presence of congenital valves, ureteroceles and "strictures" at the ureterovesical junction was readily explained by the fact that in certain instances the epithelial membrane may persist for an unduly long time.

It was pointed out that in interpreting the causative background of the various types of ureteral dilatation in infants and children the aforementioned anatomic and physiologic observations on embryos are of the greatest significance. These facts should also be borne in mind before the urologist commits himself to the diagnosis of such conditions as "segmental neuromuscular imbalance of the lower third portion of the ureter."

Recommendation was made that destruction of the membrane, if it still exists, together with adequate ureteral dilatation, with or without

29. Vermooten, V.: A New Etiology for Certain Types of the Dilated Ureters in Children, J. Urol. **41**:455-463 (April) 1939.

ureteral meatotomy, is the most conservative as well as the only treatment necessary to correct the congenital deformity.

If the process has proceeded so far that the ureteral musculature has been destroyed, the urologist cannot expect the ureter to return to normal by any operative procedure other than a plastic one.

The sooner after birth the condition is recognized and corrected the greater will be the opportunity for an eventual return to normal.

Transplantation.—Higgins,[30] in discussing the transplantation of ureters in infants, stated that the infant tolerates surgical procedures well. This tolerance is attested by the results secured by operations for intussusception, hypertrophic pyloric stenosis, strangulated hernia, cleft palate and harelip.

As the child becomes older, recurring attacks of renal infection may eventually result in renal sepsis and death. Similarly, as months or years elapse, dilatation of the lower third portion of the ureters frequently occurs, which may render transplantation into the bowel technically difficult or impossible.

It is probable that the organisms present in the colon during early infancy are less virulent than those present in later childhood or adult life. When the operation is performed at an early period in life, the child may develop normally from both the physical and the mental standpoint. Because of the unfortunate defect, the parents may become extremely attached to the child; if death should result from the operation, it is better for it to occur before such sentimental ties are established. For these reasons, Higgins expressed the belief that operation should be performed during the first few months of the patient's life. During the past year, this procedure has been carried out on 7 children less than 1 year of age, and the results have been entirely satisfactory.

After a period of preoperative preparation, operation is performed with the child under ether anesthesia and in the Trendelenburg position. The two stage operation, with employment of a modified Coffey I technic, is used. The right ureter is transplanted into the rectosigmoid portion of the colon, and approximately ten days later the left ureter is transplanted into the bowel. If the child's condition permits, the bladder is removed at the second transplantation, or this procedure may be deferred to a later time, when correction of the urethra is accomplished. The operation should extend down to the bowel. If anastomosis is performed with the bowel delivered into the incision, there is danger of kinking of the ureter, or too much tension may be exerted on the ureter when the bowel is replaced in its normal position. Instead of introducing the cut end of the ureters into the lumen of the bowel

30. Higgins, C. C.: Transplantation of Ureters in Infants, J. Urol. **41**:464-470 (April) 1939.

as the first step in the transplantation, this should be deferred until after the anchoring and transfixing sutures have been placed, thereby anchoring the ureter and closing the trough in the wall of the bowel. The ureter is then introduced into an opening through the mucosa made by a spear-point scalpel, and the final sutures are tied. After this, a complete change of gloves by the operating team is advisable.

In Higgins' 7 cases, convalescence was unusually smooth and devoid of complications, except for impetigo in the case of 1 child and disruption of the wound in another. There was no mortality, all the children leaving the hospital in a satisfactory condition.

BLADDER

Vesical Tumor.—McClelland [31] discussed endometriosis of the urinary bladder. He stated that in most cases endometriosis follows a pelvic operation on the female organs. The symptoms are cyclic in occurrence, coming immediately before and during each menstruation. There are usually pain over the region of the bladder, frequency of urination and pain at the end of urination. Hematuria is not a symptom, but blood in microscopic quantities is found in the urine during the period.

The cystoscopic picture varies from localized reddening of the mucosa to bluish cysts. The cysts are contained in a puckered region of the bladder and are covered by mucosa. During the intermenstrual period there is a decrease in the size of the mass.

Treatment is directed to removal of the ovarian hormonal influence. Sterilizing doses of roentgen rays or surgical removal of the ovaries causes disappearance of these symptoms.

McClelland reported 1 case of the condition involving a woman of 41. She had had tenderness over the region of the bladder, in the midline. Four months previously she had had cesarean section for termination of a three months' pregnancy, with ligation of the tubes. She had moderate frequency and slight dysuria. At the first examination, cystoscopy revealed nothing abnormal. Later, cystoscopy revealed an area of redness in the right lateral wall of the bladder. Vaginal examination disclosed a small lump, the size of a walnut, lying to the right of the uterus. At operation the uterus and ovaries were involved by adhesions, but no evidence of endometriosis was observed in the peritoneal cavity. The peritoneum was then folded back, and a lump was felt in the region of the uterus. The lump was resected extraperitoneally. The pathologist's report showed this mass to be endometriosis of the urinary bladder.

This patient had had a pelvic operation, which was followed immediately by vesical symptoms. A lesion was not seen inside the bladder

31. McClelland, J. C.: Endometriosis of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **31**:215-219, 1938.

until cystoscopic examination four years later, at which time a region of localized redness was noted. Later, the bluish cystlike bodies were seen in the region of localized redness three years before. The absence of endometrial tissue in the peritoneal cavity led to a change of diagnosis during the operation and to resection of the localized lump in the bladder. If endometrial implants had been found, oophorectomy would have been sufficient and resection would not have been necessary.

Reynolds [32] stated that the possibility of endometriosis of the bladder should always be considered in treatment of a patient suffering from frequency of urination, dysuria and hematuria. When this triad is cyclic and is exacerbated during the menstrual period, the necessity for urologic consultation should be brought to the attention of the general practitioner. If the urologist finds at cystoscopic examination that "blue-black cysts and endometriostic edema" are present, the diagnosis of endometriosis of the bladder is certain. The method of choice in the treatment of vesical endometriosis is the induction of artificial menopause with roentgen rays. Surgical intervention, however, is indicated in the few cases in which the patient is considerably under the menopausal age and desires children.

Ewell [33] stated that small, nonspecific infective granulomas occurring in the urinary tract, especially in the bladder and urethra, are frequent. A granuloma of the type and size of the lesion in the case reported by Ewell is rare, since a review of the literature does not disclose a similar case. In his case there had been seen at laparotomy, two years previously, extensive mesenteric lymphadenitis, the patient giving a long history of repeated attacks of tonsillitis, which suggested that the tonsils were the focal point of infection and that the infection was an etiologic factor in both processes. Lesions of the type reported on by Ewell are of importance for several reasons, the chief being that they are frequently mistaken for neoplasms. Partial removal of the lesion and prolonged vesical drainage have produced temporary cure.

Colby [34] reported on a small group of malignant tumors of the bladder which were treated by supervoltage roentgen rays with a recently devised 1,000,000 volt generator. Although Colby considered the series inadequate for fair evaluation of this form of treatment, certain tumors appear to be profoundly affected by it and exhibit considerable regression. The portions of the tumor which project into the vesical cavity seem to be affected considerably more than those which have extended

32. Reynolds, L. R.: Endometriosis of Bladder, J. Urol. **41**:157-163 (Feb.) 1939.

33. Ewell, G. H.: Non-Specific Infective Granulomata of the Bladder: Case Report, J. Urol. **41**:627-637 (April) 1939.

34. Colby, F. H.: Super-Voltage Radiation in the Treatment of Bladder Tumors, Tr. Am. A. Genito-Urin. Surgeons **31**:227-244, 1938.

through the vesical wall. Other tumors are affected little, if any, and are considered to be "radioresistant." It is not considered that supervoltage irradiation, in its present state, takes the place of operation in instances of circumscribed cancer which can be adequately removed. The dose thus far employed is probably considerably less than that which it is possible to use, but more experience is necessary before the dose can be standardized and its ultimate effect determined. Local and generalized untoward reactions are less than those accompanying lower voltages, and regression of the tumors is more evident.

Kretschmer and Doerhing [35] described a case of leiomyosarcoma of the urinary bladder. A summary of 14 cases of this condition was given, in 8 of which the diagnosis was positive and in 6 of which the tumor was described but was not diagnosed as leiomyosarcoma. Leiomyosarcoma usually afflicts patients under the age of 12 years or more than 45. In most instances, the lesion arises from the wall of the bladder. Metastasis is rare. Although in the case reported the tumor was enormous, Kretschmer and Doerhing called attention to the fact that the cystographic appearance of the bladder was normal. The correct diagnosis was not made until the specimen taken at necropsy had been carefully studied.

Priestley and Sawyer [36] discussed two stage total cystectomy for carcinoma of the bladder and reviewed several recent cases which had been reported in detail. They emphasized that total cystectomy can be performed with reasonable operative risk and that the results compare favorably with those of operative procedures for the removal of malignant growths from other organs in the body. When both ureters are transplanted into the bowel, the patient may lead a normal and comfortable life, providing the ureteral anastomosis functions satisfactorily. When, in exceptional cases, cutaneous ureteral transplantation is performed, the patient may not be so comfortable, but cutaneous transplantation of the ureters possesses no more undesirable features than does colostomy, which has been an accepted procedure for a number of years. Indications for total cystectomy are not as yet standardized. In the past, the operation was reserved largely for patients who had high grade or recurrent lesions, and who undoubtedly had regional or distant metastases. In some cases in which the bladder was removed under these circumstances, satisfactory end results could not be anticipated, and were not obtained.

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35. Kretschmer, H. L., and Doerhing, P.: Leiomyosarcoma of the Urinary Bladder, Arch. Surg. **38**:274-286 (Feb.) 1939.

36. Priestley, J. T., and Sawyer, M. H.: Two-Stage Total Cystectomy for Carcinoma of the Bladder: Report of Two Recent Cases, Proc. Staff Meet., Mayo Clin. **14**:65-68 (Feb. 1) 1939.

Priestley and Sawyer expressed the belief that during recent years indications for total cystectomy have undergone a gradual change. At this time it is considered that the bladder may be removed wisely in some cases of very large low grade neoplasms or repeatedly recurring low grade neoplasms which cannot be controlled satisfactorily by less radical measures. High grade lesions which, to the best of the surgeon's knowledge, are still confined to the bladder may also be treated by complete removal of the bladder. Total cystectomy is performed preferably in two stages. Simultaneous bilateral ureterosigmoidostomy is performed as the first stage, and subsequently the bladder is removed. In exceptional cases, when cutaneous ureteral transplantation is performed, the entire procedure, including removal of the bladder, may be accomplished in one stage. The three stage operation is usually not desirable.

Lidzki [37] stated that dermoid cysts of the bladder are extremely rare. The number of cases thus far published does not exceed 15. These cysts may exhibit the symptoms of cystitis and offer as a pathognomonic sign the discharge of hairs on urination (pilimictio). Such a cyst may occur as a tumor protruding into the vesical cavity, or as a paravesical cyst which invades the bladder and communicates with it through a small channel, as was the case in the instance reported. The treatment consists in removal of the cyst, either by an intravesical or extravesical procedure or by a combined approach.

Lidzki reported a case of a woman aged 30 who suffered from intractable cystitis. Cystoscopic examination was impossible. Roentgenologic examination disclosed two shadows in the pelvis. Cystostomy revealed that one of the shadows corresponded to a stone, the other to a ball of hair. The latter lay in a diverticulum which represented a paravesical dermoid cyst that had opened into the bladder. The cystovesical, fistulous tract having been dilated and its contents removed, the cyst became practically obliterated.

Calculus.—Twinem [38] reviewed the cases of vesical calculus involving patients treated at the New York Hospital since 1820. The operative mortality in the earliest period, from 1820 to 1846, when perineal lithotomy was routinely employed, was 10 per cent. This mortality then increased greatly in the next two periods, between 1847 and 1866 and between 1866 and 1920, but since 1920 it has been only 5.4 per cent. The mortality from litholapaxy has consistently been too high, although it has decreased markedly since 1920.

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37. Lidzki, A.: Dermoid Cyst of the Bladder: Case Report, Ann. Surg. **109**:274-276 (Feb.) 1939.

38. Twinem, F. P.: Surgical Removal of Vesical Calculus: An Experimental and Clinical Study, J. Urol. **41**:360-365 (March) 1939.

Twinem expressed the belief that the choice of operation in cases of vesical calculi depends on the age and physical condition of the patient, the size and hardness of the stone, the presence or absence of urethral stricture or associated prostatic hypertrophy and the experience of the surgeon. More skill is required to perform litholapaxy properly than is needed for suprapubic lithotomy. Crushing possesses two advantages over cutting: (1) a shorter convalescence and (2) a lower mortality rate. At the New York Hospital the mortality rate for litholapaxy between 1847 and 1920 was very high (22 to 25 per cent). Since the organization of the Brady Foundation, in 1920, the operative mortality has decreased to 8.1 per cent, which is still much too high. The mortality for suprapubic lithotomy has been reduced to 5.4 per cent. It is believed that the operative mortality for patients subjected to litholapaxy has been excessive and that it can be greatly reduced by attention to details of proper technic.

A study of the 7 cases of death following litholapaxy among patients operated on from 1866 to 1920 shows the large part played by vesical traumatism, for 3, and probably 4, of these 7 deaths were caused by rupture of the bladder.

Stenosis of the Vesical Neck.—Irwin [39] reported on the operative treatment of patients having stenosis of the vesical neck. In all, he reviewed 48 cases in which operation was carried out by means of a clamp-incisor.

The bladder is exposed by a vertical suprapubic incision 2½ inches (about 6 cm.) in length, and is then opened. A finger of the surgeon's left hand, on which two gloves are worn, is passed into the rectum and presses the vesical neck forward, while the index or middle finger of the gloved right hand is pushed through the vesical neck into the prostatic portion of the urethra. The finger of the right hand is now forced down in front of and below the posterior part of the vesical sphincter, and continued backward below the anterior part of the trigon. The clamp-incisor, which Irwin designed in 1929, is applied, and the blade is pushed down the grooves to the end of the instrument. In this way, the posterior part of the internal sphincter and the center of the trigon for about 1 inch (2.5 cm.) are not only divided, but also thoroughly crushed on each side of the incision. After division of the sphincter and the adjacent part of the trigon, the cut edges are drawn back, leaving a large opening in the vesical neck and a wide vertical gutter, thereby causing the outlet of the bladder to be situated on a much lower plane.

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39. Irwin, W. K.: The Operative Treatment of Stenosis of the Vesical Neck, Brit. J. Surg. **26**:764-767 (April) 1939.

Irwin listed the advantages of this technic. A short suprapubic incision is sufficient. The operation can be performed in two stages, the subsequent division of the sphincter and trigon being carried out without enlarging the preliminary opening made during cystotomy. The method is simple, and the operation is quickly performed. The procedure is safe and free from postoperative complications. There need be no fear of hemorrhage or sepsis. The treatment is curative; in this series of 48 cases, Irwin did not see any patient who had recurrence of the obstruction at the vesical neck. If there is any adenomatous tissue in the prostate gland, it can be enucleated during the course of the operation.

Cystostomy.—Keyser [40] described a simple technic for incising the bladder suprapubically for drainage. He makes a 1 inch (2.5 cm.) incision, 1 inch above the symphysis, proceeding with the use of local anesthesia. After blunt separation of the muscles and transversalis fascia, a large Hirschman anoscope is introduced. With reflected light, the anoscope provides a 1 inch circular field, through which the peritoneal fold is dissected upward with a Kuttner roll until the wall of the bladder is exposed. The bladder has been previously distended with a solution of methylthionine chloride U. S. P.; the site of puncture is accurately located by means of an aspiration syringe. This region is seized with Allis clamps, and the portion of bladder held between these clamps is incised sufficiently to admit the introduction of a no. 24 F catheter.

If severe infection exists, the operation is carried out in two stages. At first the wall of the bladder is exposed as described previously, and the region is packed through the anoscope with acriflavine gauze. After twenty-four to seventy-two hours the gauze is removed, and two narrow Richardson retractors are placed to spread the incision and bring the bladder into view, at which stage it is perforated and the drainage catheter is placed in position.

In closing the incision, one stitch may be placed inferiorly, between the bladder and the fascia above the symphysis, closing the space of Retzius. Through and through silkworm sutures, including muscle, fascia and portions of skin on each side, one above and one below the catheter, close the wound and complete the operation. No other drainage is used.

The operation as performed in 7 instances has been shown to be of advantage, since there was no shock, pain or elevation in temperature. It affords opening the bladder under vision, with exposure of a minimal amount of raw surface to infection or urine. It also avoids possible

40. Keyser, L. D.: Suprapubic Cystostomy by an Endoscopic Technique, J. Urol. **41**:228-233 (Feb.) 1939.

perforation of the peritoneum or intestine. The procedure has not been attended by infection of the space of Retzius or perivesical infection with urine.

Transurethral Operation.—Thompson [41] presented a series of 24 cases of dysfunction of the vesical neck in women, in which 35 transurethral operations were performed.

The causative background of this disease is not definitely revealed by histologic study of the tissue removed by transurethral operation. The hypothesis that it is caused by fibrosis in the sphincteric region seems fallacious in view of the fact that a considerable amount of fibrosis is observed in normal tissue taken from this region. A possible explanation of the condition is that hyperplasia of the superficially lying epithelium or of the vesical sphincteric muscle occurs and causes urinary retention.

The results of operation have been classified as excellent in 14 cases, good in 5 cases, fair in 4 cases and poor in 1 case.

Removal of tissue from the entire circumference of the vesical neck is necessary to obtain a good result in all but those exceptional cases in which incision alone may suffice.

Observation of the patient by the urologist for a number of years after operation is advisable, and treatment, including dilatation with a Kollmann dilator, will probably be necessary in some cases in order to maintain normal vesical function; the transurethral operation can be repeated with benefit if urinary obstruction recurs.

O'Conor [42] stated that small vesicovaginal fistulas with healthy surrounding tissue will heal after electrocoagulation, if postural drainage can be maintained with an indwelling catheter for a sufficient period. The possibility of utilizing this method should receive more consideration, especially in the case of patients on whom unsuccessful surgical repair has resulted in a small lateral opening. The method obviously has no place in the treatment of fistulas of the floor of the bladder or in that of extensive defects of the tissues.

Sympathectomy.—Nesbit and McLellan [43] stated that sympathectomy relieves vesical pain, not by removing the essential afferent pathways leading from the viscus but by relieving spasm of the internal vesical sphincter, and perhaps other parts of the vesical musculature. Certainly, the one constant and predominating feature in all the cases of Nesbit and

41. Thompson, G. J.: Transurethral Operations on Women for Relief of Dysfunction of the Vesical Neck, J. Urol. **41**:349-359 (March) 1939.

42. O'Conor, V. J.: Non-Surgical Closure of Vesicovaginal Fistula, Tr. Am. A. Genito-Urin. Surgeons **31**:255-259, 1938.

43. Nesbit, R. M., and McLellan, F. C.: Sympathectomy for the Relief of Vesical Spasm and Pain Resulting from Intractable Bladder Infection, Surg., Gynec. & Obst. **68**:540-546 (Feb. 15) 1939.

McLellan's series was vesical spasm prior to operation. Likewise, the one constant postoperative result was relief from intolerable spasm and ease of urination.

It further appears evident that section of the hypogastric nerves alone, without the more extensive and hazardous division of the lateral sacral sympathetic nerves, provides relaxation of the sphincter adequate to relieve spasm of the bladder.

Since normal afferent components exist in the bladder after sympathectomy, it appears illogical to suppose that vesical pain resulting from a malignant growth would be relieved by this operation.

In conclusion, Nesbit and McLellan repeated:

1. The parasympathetic (sacral) pathways carry the essential afferent components of the bladder.

2. The sympathetic (presacral, or hypogastric nerves) pathways may or may not carry afferent pain components of the bladder.

3. Division of the presacral nerves provides relief of vesical spasm and pain resulting from intractable vesical infections.

4. Division of the lateral sacral sympathetics in addition to [division of] the presacral nerves accomplishes this same end but does not appear to be necessary or desirable.

5. Sympathectomy brings about the relief of spasmodic pain by relaxation of the vesical outlet and the detrusor mechanism; it does not render the bladder insensitive to pain of other origin.

6. Sympathectomy for the relief of vesical pain should be resorted to only [for] those patients [whose] pain is clearly demonstrated to result from spasm of the vesical outlet.

7. Sympathectomy was not shown to cure the lesions of Hunner ulcer in the cases here reported.

Incomplete Emptying—Kirwin and Hawes [44] stated that the amount of residual urine is never constant and under different conditions may vary considerably. Their experiments indicated that any male above the age of puberty may have residual urine if the bladder is overdistended. In the presence of intravesical or intraurethral prostatic intrusion, if the bladder is overdistended acute retention is likely to develop. The amount of residual urine cannot serve as an indication for the employment of any particular method of surgical intervention directed at the prostate gland. Demonstration of residual urine is not in itself sufficient indication for the performance of operations on the vesical neck. Determinations of the residual urine should be carried out with greater accuracy than is the usual practice at present.

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44. Kirwin, T. J., and Hawes, G. A.: The Diagnostic Value of Residual Urine Estimation, J. Urol. **41**:413-429 (March) 1939.

URACHUS

Cysts.—Kantor [45] stated that the most frequent abnormalities of the urachus are anomalies in development and formation of cysts, which may at times be related to congenital defects. Long classified cysts of the urachus into four anatomic groups—those which communicate with the bladder; those which communicate with the umbilicus; those which communicate with the bladder and umbilicus, forming vesicoumbilical fistulas, and those which do not seem to communicate with either structure.

Kantor limited his study, for the most part, to cysts which do not seem to communicate with either the bladder or the umbilicus. Patients having such cysts frequently present the diagnostic problem of differentiation of a midline suprapubic mass which is only slightly movable.

The incidence of cysts of the urachus is rather low. In 1886 Lawson Tait presented 12 cases of suprapubic cysts, several of which were without doubt urachal in origin. All the cysts were described as lying extraperitoneally. In 2 of these cases excision was attempted, which resulted in immediate fatality. In the remainder, incision and drainage were effected, with no immediate mortality, although several deaths were noted later. Among the patients who lived, Tait did not describe any subsequent recurrences. He was probably the first surgeon to diagnose this condition preoperatively.

In reviewing the literature on cysts of the urachus, it is found that the diagnosis is usually made at operation. After the usual suprapubic incision, the mass is observed to be extraperitoneal, and its origin from the urachus is frequently obvious. Because of the conception held by some surgeons that complete extirpation is necessary for cure, Kantor described the following cases:

A girl of 2 years was moderately ill. In the suprapubic region, and extending midway to the umbilicus, was a round, tender, cystic mass, the size of an orange. During the examination the child expressed a desire to void and passed a small amount of urine. A midline suprapubic incision was made into a cyst which contained about 8 ounces (237 cc.) of thick, creamy pus. Evacuation of the contents revealed a smooth-walled cavity, from which a specimen for biopsy was taken. The cyst was drained. The interesting point in this case was that the wound healed completely and the child became well after simple drainage. Excision of the cyst was unnecessary. When the patient was seen in the follow-up clinic six months later, the scar was firm and there was no evidence of recurrence of herniation. The cure effected by this simple procedure was unquestioned.

45. Kantor, H. I.: Cysts of the Urachus: Report of Two Cases, Ann. Surg. **109**:277-285 (Feb.) 1939.

Kantor reviewed 36 reported cases. In 7 cases cure followed incision and drainage of the cyst. In all but 1 case infection was present. Three instances of incomplete excision with cure were noted. No recurrences in these cases have been reported.

Four cases of fatality subsequent to excision are recorded. In 3 of these peritonitis was given as the cause of death.

Four cases of excision secondary to initial incision and drainage were reported. In 3 of these complicating features may have prevented normal healing.

In many of the reports, technical operative difficulty was noted in cases in which primary excision was performed. Adherent peritoneum was frequently excised, with occasional difficulty in closure. The bladder was opened in several instances. In 1 case reported attempt at excision would have been futile.

PROSTATE GLAND

Enlargement.—Deming and Neumann,[46] in a study of the early phases of prostatic hyperplasia, concluded that the early change of benign enlargement of the prostate in man is primarily a multiplication of fibromuscular elements. It resembles in its early stages the uterine fibromyoma, which is derived from muscle cells of the uterus. Since the posterior portion of the urethra and the internal vesical sphincter contain muscle fibers which are derived from the same embryologic building material as that of the uterus, it is fair to assume that these two tumors have the same origin. It is probable that the solid nodule produces a stimulating and proliferating effect on the epithelium of the wall of the duct, causing the epithelium to invade the solid nodule and form glands within it. The fibromyomatous tissue is invaded and overgrown by a more rapidly growing duct and glandular tissue, with the result that the nodule in its later stages has the appearance of an encapsulated glandular tumor. Benign prostatic enlargements are not the result of hypertrophy, but are caused by true hyperplasia, derived from muscle, fibrous tissue and ducts.

Davis [47] stated that, although resection is the shorter procedure, prostatectomy is both safer and surer. Resection usually takes less time than prostatectomy as measured by the number of days spent by the patient in the hospital, but not as measured by the number of days of convalescence or by actual operating time. Perineal prostatectomy is decidedly safer than resection in the hands of some surgeons, although there is no essential difference when the best available mortality figures for each procedure are compared. In good hands prostatectomy by

46. Deming, C. L., and Neumann, C.: Early Phases of Prostatic Hyperplasia, Tr. Am. A. Genito-Urin. Surgeons **31**:339-350, 1938.

47. Davis, E.: Prostatectomy or Transurethral Prostatic Resection? A Plea for the Selectionist, J. A. M. A. **112**:681-687 (Feb. 25) 1939.

either route is surer than resection in that the majority of surgeons agree that enucleation gives more dependable assurance of complete and permanent symptomatic relief.

Patients are well served and good results are obtained by skilful extremists of both groups. The mortality rate and the functional results of transurethral resection bear a definite relation to the skill and experience of the surgeon. The consensus indicates that the public demand for transurethral resection is showing a tendency to decrease. The number of urologists who are tending to decrease their percentage of resections is distinctly greater than the number tending to increase this percentage.

The chief, if not the sole, advantage of resection in the best hands over perineal prostatectomy in the best hands consists in the saving of from nine to fourteen days of postoperative hospital care. Transurethral resection, after having passed through a typical cycle of trial and appraisal, including both abuse and overcorrection, is now approaching the final stage of stability, with a clearly defined field of usefulness.

Nesbit [48] stated that transurethral prostatectomy, when properly performed, shows to advantage over other types of prostatectomy in that it is accompanied by a very low mortality rate, lessened morbidity and a greatly reduced period of hospitalization. An important advantage to the patient is that he is saved the distress and discomfort attendant on the wounds incident to open operations.

Transurethral prostatectomy is a sound procedure which demands a high degree of technical skill for its proper execution. Any surgeon possessed of this skill can perform the operation with the expectation of obtaining excellent postoperative results. Such a surgeon will recognize the limits of his own dexterity and will perform the operation only in those cases in which he can expect to carry out a rather complete prostatectomy. Other cases he will reserve for more appropriate surgical procedures.

The able resectionist will guard his patients against morbidity and death from needless loss of blood and from sepsis, since these complications have been largely eliminated by modern surgical methods. He will prevent the occurrence of traumatic stricture as a devastating sequel to an otherwise satisfactory prostatectomy.

Refinements in technic and improvements in the surgeon's armamentarium have increased the scope of usefulness for transurethral prostatectomy and have tended to decrease the limitations on it.

Powell [49] stated that, notwithstanding the wide use of anterior pituitary-like gonadotropic substance from the urine of pregnant women

48. Nesbit, R. M.: Some Refinements in the Technic of Transurethral Prostatectomy, J. A. M. A. **112**:687-689 (Feb. 25) 1939.

49. Powell, T. O.: Precocious Hypertrophy of Prostate Following Persistent Treatment with Gonadotropic Hormone, J. Urol. **41**:206-209 (Feb.) 1939.

in the treatment of boys having undescended testes, there have been no reports in which abnormal prostate glands developed in these patients.

He reported a case in which a youth aged 17 was treated weekly for one year with a preparation containing the gonadotropic principle from the urine of pregnant women. The prostate gland as palpated per rectum and as seen through the cystoscope seemed definitely hypertrophied. There was 150 cc. of residual urine. The symptoms were typical of prostatism, with the addition of frequent abnormal erections of the penis. The hormonal treatment had failed to cause the testes to descend, and orchidopexy had been performed, with success.

The condition of the patient was followed for two years, at the end of which time his symptoms had greatly subsided and cystoscopic examination revealed only a mild glandular bar at the neck of the bladder. There was no residual urine.

Powell concluded that, on the basis of experimental information, it was the continued treatment with gonadoprostatotropic substance that caused the precocious hypertrophy of the prostate gland in this case.

On the basis of analysis of the blood of 73 patients, Boyd and Berry [50] obtained evidence of the presence of lipopenia in cases of prostatic hypertrophy. The feature of this lipopenia was a decrease of 30 to 40 per cent in the concentration of total lipids, total cholesterols, ester cholesterol and phospholipid in the plasma. There was no significant alteration in the lipid content of the erythrocytes. For 20 patients who had elevated concentration of blood urea the lipid values of the plasma were not significantly different from those of 20 other patients who had no elevation in the concentration of blood urea. The condition was termed the "lipopenia of prostatism."

In conjunction with the results of recent experimental studies of the endocrine glands which have been reviewed, this evidence indicates that enlargement of the prostate gland must be considered part of a general metabolic disturbance. Lipopenia may now be offered as an additional feature of prostatism. Determination of the concentration of cholesterol or phospholipid in the plasma may be used as an index of the efficacy of various forms of treatment other than prostatectomy.

Gundersen [51] stated that a satisfactory result in treating the aged patient who has prostatic disease depends largely on the skill and experience of the surgeon. Urethral trauma must be minimized by shortening

50. Boyd, E. M., and Berry, N. E.: Prostatic Hypertrophy as Part of a Generalized Metabolic Disease: Evidence of the Presence of a Lipopenia, J. Urol. **41**:406-412 (March) 1939.

51. Gundersen, A. H.: Management of Prostatic Disease in Persons Past Seventy-Five: A Report of Seventy-Five Cases with End Results, J. A. M. A. **112**:833-835 (March 4) 1939.

the operating time; hemorrhage must be under control at all times. Supportive transfusions of blood should be given more frequently to old than to young patients. Whenever possible, the entire obstruction should be removed in one operation; a second resection is often poorly tolerated. Asepsis, adequate removal of all obstruction and meticulous care of the draining catheter are even more important in older than in younger patients. Gundersen expressed the belief that sulfanilamide is of value when given preoperatively as a prophylactic against infection. Despite the fact that men of more than 75 who have prostatic obstruction are precarious operative risks, resection offers them relief from suffering and a comfortable life so far as the bladder is concerned. There will always be a mortality, but with care and proper management the rate can be kept surprisingly low.

Of 12 patients with prostatic hypertrophy reported on by Moore, Keyes and McLellan [52] who were treated by roentgen irradiation, 6 required prostatectomy within two years; 4 were either improved or in equilibrium with the disease after three years; 1 died of an intercurrent disease, and the fate of 1 is unknown. In 5 instances the prostate gland, studied histologically, revealed only minimal changes that might be attributed to roentgen irradiation. These changes were slight periacinar fibrosis and relative absence of lymphoid tissue and evidences of inflammation.

Belt, Ebert and Surber [53] described a new anatomic approach in perineal prostatectomy.

A curving transverse perineal incision, 1.5 cm. from the anal mucosa, exposes the delicate fibers of the median raphe. These fibers are cut, revealing the arching fibers of the external rectal sphincter muscle, which are raised to disclose the glistening longitudinal muscular layer of the rectum. The anal canal and rectum are depressed and pushed backward, defining the central tendinous plane of the perineum. The areolar tissue and tendinous portion of the rectourethralis muscle, joining the rectum to the base of the perineal membrane, are snipped through, revealing the anterior free borders of the levator ani muscles and the flat sheath of the rectourethralis muscle. The rectourethralis muscle is split medially and is retracted laterally with the levator ani muscles, exposing the tough, white, shining fascia of Denonvilliers covering the posterior surface of the prostatic capsule. By using, therefore, the cleavage plane present between the external sphincter ani muscle and the longitudinal

52. Moore, R. A.; Keyes, E. L., and McLellan, A. M.: Histologic Studies of the Effect of Irradiation on Hypertrophy of the Prostate, Tr. Am. A. Genito-Urin. Surgeons **31**:371-382, 1938.

53. Belt, E.; Ebert, C. E., and Surber, A. C., Jr.: A New Anatomic Approach in Perineal Prostatectomy, J. Urol. **41**:482-497 (April) 1939.

muscle fibers of the rectum, the capsule of the prostate gland is exposed bloodlessly and without cutting a nerve.

Preoperative Mortality.—Engel [54] called attention to the preoperative mortality accompanying prostatic obstruction. Forty patients, or 74 per cent of 54 persons studied, Engel felt, died unavoidably, while in the case of 14 patients, or 26 per cent, death might have been prevented. This study emphasizes the potential danger attendant on the first catheterization of a patient suffering from acute urinary retention, a danger which those of the general medical profession must not ignore. Engel condemned use of the inlying catheter as a routine method of preoperative drainage; he has reduced the preoperative mortality by substituting suprapubic puncture or regular intermittent catheterization. The preoperative methods outlined have not only reduced the preoperative mortality and morbidity, but have also resulted in a smoother postoperative convalescence and a reduction in the operative mortality.

Tumors of Connective Tissue.—Wyler [55] described leiomyoma of the prostate gland afflicting a man aged 37. The history and symptoms were similar to those occurring in the presence of benign hypertrophy of the prostate gland. Perineal prostatectomy was performed. Microscopic observation did not show any signs of malignant degeneration, and the patient had not had recurrence two years after prostatectomy. This is the fourth case of true leiomyoma reported.

Smith and Mintz [56] stated that rhabdomyosarcoma of the prostate gland is a rare disease. Twelve cases have been found in the literature, and Smith and Mintz reported an additional case. In 49 per cent of the cases the tumor involved children less than 10 years of age; in all but 1 case the patients were less than 32 years of age. The meager evidence at hand tends to prove that rhabdomyosarcoma is very radioresistant. The tumors tend to recur locally, and in the terminal stage metastasize by cellular dissemination through the blood. No instance of cure has been reported.

Sarcoma.—Stirling and Ash [57] added to the 132 cases of sarcoma of the prostate collected by Lowsley and Kimball. They summarized the data of 35 recently published cases and added 5 cases of their own. The data were discussed briefly from the standpoint of the clinical

54. Engel, W. J.: Preoperative Prostatic Mortality, J. Urol. **41**:505-514 (April) 1939.

55. Wyler, J.: Leiomyom der Prostata, Schweiz. med. Wchnschr. **69**:339-340 (April 15) 1939.

56. Smith, G. G., and Mintz, E. R.: Rhabdomyosarcoma of the Prostate in a Boy Seven Years of Age: Review of the Literature, Tr. Am. A. Genito-Urin. Surgeons **31**:351-362, 1938.

57. Stirling, W. C., and Ash, J. E.: Sarcoma of the Prostate, J. Urol. **41**:515-533 (April) 1939.

picture and treatment, and more extensively from that of pathologic changes. Stirling and Ash reached the following conclusions:

1. Sarcoma of the prostate gland is not necessarily a tumor of early life.

2. The diagnosis is easier in the earlier age groups because of the diminished likelihood of the presence among such patients of carcinoma and benign hypertrophy.

3. Sarcomas in the earlier age groups are more malignant, metastasizing more freely and running a more fulminant course.

4. In all age groups sarcomas of muscular origin are the most common, and the existence of primary lymphosarcoma of the prostate gland has not been proved. It is likely that a number of the tumors reported as round cell sarcomas are in reality undifferentiated small cell carcinomas.

5. While treatment is still of little avail, it is felt that, particularly in older patients, prostatectomy is most important if it can be carried out before metastasis has occurred.

6. The symptoms are largely those of urethral and rectal occlusion, none being of much aid in differential diagnosis.

7. In the old patient the prostate gland is firm, smooth and difficult to differentiate from a gland which has undergone benign hyperplasia, in contrast to the fixed, hard, nodular prostate gland invaded by carcinoma.

8. Although in the presence of metastasis death can be attributed directly to the tumor, in the majority of cases death is caused by secondary complications, chiefly urinary obstruction and infection, as also is true in cases of benign hypertrophy of the prostate gland and carcinoma of the bladder.

Massage and Blood Pressure in Cases of Prostatic Infection.—Hammer and Schulte [58] stated that certain patients exhibit mild or marked vasomotor collapse after prostatic massage. In order to determine what physiologic changes are responsible for this occasional development, observations were made on the pulse rate and blood pressure of 378 unselected patients. In this series only 38 patients had lesions of the prostate gland other than prostatitis. There was no significant difference in the vasomotor response, regardless of the condition in the prostate gland. Likewise, differences in the observations depending on posture of the patient were negligible.

In 4 of the 378 cases syncope occurred after massage of the prostate gland. The average blood pressure prior to massage in these 4 cases

58. Hammer, H. J., and Schulte, T. L.: Blood Pressure Changes Produced by Prostatic Massage, Proc. Staff Meet., Mayo Clin. **14**:13-15 (Jan. 4) 1939.

was 125 mm. of mercury systolic and 75 mm. diastolic. After massage the average pressures were 62 mm. of mercury systolic and 41 mm. diastolic.

Of the entire group, 38 patients were less than 30 years of age; 304 were from 30 to 60, and 36 were more than 60. This last group was the smallest, but showed the highest percentage of extreme response (38 per cent). The first group had an average control blood pressure of 119 mm. of mercury systolic and 76 mm. diastolic; the second group, a pressure of 124 mm. of mercury systolic and 79 mm. diastolic, and the third group, a pressure of 138 mm. of mercury systolic and 93 mm. diastolic. After massage, the average blood pressures for the three age groups were, respectively, as follows: 123 mm. of mercury systolic and 86 mm. diastolic, 132 mm. of mercury systolic and 86 mm. diastolic and 157 mm. of mercury systolic and 106 mm. diastolic.

Of 378 cases, there were increases in systolic or diastolic pressure in 284 (75 per cent). Of the entire group, there were 89 cases (23 per cent) in which there was a decrease of both systolic and diastolic pressure. All patients had an increase in pulse rate, the average being 16 per minute. Of this series, there were 76 patients (20.1 per cent) for whom hypertension might be predicted on the basis of a hyperresponse to prostatic massage in both systolic and diastolic blood pressure. Thirty-one patients in the series had essential hypertension. Of these, 18 patients (58.06 per cent) showed an extreme response, and only 3 patients exhibited minor decreases in both systolic and diastolic pressure.

In the 50 cases in which both prostatic massage and the cold pressor test were used, it was found that as a result of massage the average increase in systolic pressure was 22 mm. of mercury and in the diastolic 20 mm. of mercury. The average increase in pulse rate was 23 per minute. As a result of the cold pressor test, the average increase in systolic pressure was 19 mm. of mercury, and in the diastolic, 16 mm. of mercury. The average increase in pulse rate was 3 per minute. After massage 18 patients (36 per cent) had a hyperresponse, although in the cold pressor test there were 13 patients who had such a response. In the 13 cases in which there was a hyperresponse to the cold pressor test there also was a hyperresponse to massage.

The considerable elevation in blood pressure produced by prostatic massage in patients who had essential hypertension should be taken into consideration when such a procedure is undertaken.

TESTICLE

Tumors.—Quinby [59] reviewed a series of 26 cases of testicular tumor reported from the urologic clinic of the Peter Bent Brigham Hospital.

59. Quinby, W. C.: Clinical Aspects of Testicular Tumors, Rhode Island M. J. **21**:119-121 (Aug.) 1938.

He stated that although in earlier years in instances of testicular tumor attempts were made to remove the region of lymphatic drainage in the abdomen, as an addition to orchidectomy, further anatomic knowledge of the region of lymphatic drainage has shown this procedure to be hardly feasible. Also, during the past decade it has been shown definitely that many of these tumors are especially sensitive to irradiation with high voltage roentgen rays or with radium. The accepted treatment today, therefore, is that of immediate removal of the testicle by section of the spermatic cord at the external inguinal ring, followed by one or two courses of high roentgen voltage irradiation applied to the whole abdomen as high as the level of the kidney.

Seven of Quinby's patients were living without apparent recurrence, 2 of them after a period of as long as nine and ten years, respectively; 2 were living, but since operation had had metastases which had been caused to disappear with high voltage roentgen ray therapy; 2 died, 1 five and the other eleven years, after the onset of cardiorenal or circulatory disease not related to the neoplasm. Thus, there were 11 patients of 26 who were living or who died without recurrence. Fifteen patients died—2 of them with recurrence of the "hurricane type"—within two months of operation, and 6, within one year after operation. Four patients survived operation for from one and a half to four years, dying of recurrence.

Of the surviving patients, 4 had no treatment other than orchidectomy, and were still well.

Roentgen ray therapy was administered intensively, without effect, to 12 of the patients, who died. For 2 patients roentgen ray therapy seemed to have held the disease definitely in check.

Mackenzie and Ratner [60] stated that tumors of the testis metastasize early by the way of the lymphatic vessels and blood vessels. The lymphatic spread is achieved along the glands of the spermatic cord, up along the retroperitoneal group of glands, thence to the mediastinal glands and finally to the supraclavicular region on the left side. Metastases via the blood stream probably result from invasion by the tumor of the pampiniform plexus of veins. Metastases from tumors of the testis occur long before there is any clinical evidence of them.

MacKenzie and Ratner expressed the belief that every patient having a tumor of the testis must be examined periodically, at least three times a year, and that a careful search must be made for metastases, including roentgenologic examination of the thorax. If a secondary growth is discovered immediate irradiation must be instituted.

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60. MacKenzie, D. W., and Ratner, M.: Metastases from Tumors of the Testis, J. Urol. **41**:592-608 (April) 1939.

A quantitative estimation of the concentration of the follicle-stimulating principle in the urine should be made in every case of suspected tumor of the testis, and periodically in the case of every patient known to have had a testicular growth. A negative result, however, does not exclude the presence of testicular growth or metastases.

The prognosis for a patient having a testicular growth must be determined not only by the biologic response of the tumor to irradiation, but also by the clinical picture and by a careful histopathologic study of the growth.

Intensive irradiation should be administered in all cases of metastases. If the tumor is radioresistant, prolonged irradiation with smaller doses, according to the method of Coutard, is recommended.

Since the use of high voltage roentgen ray therapy, the prognosis and outcome in cases of tumors of the testis, including even those in which there are metastases, have been better.

Dean [61] stated that in a series of 39 patients seen within three months of the first symptom, he found metastases in 67 per cent. Although this figure demonstrates exceedingly high malignancy, study of approximately 600 patients who had teratomas led him to believe that the fulminating condition, in which small primary tumors throw out showers of metastases, especially through veins, is an exceptional deviation from the average natural history of the disease and that in the majority of cases there is an opportunity for application of effective treatment before metastases become too widespread.

While it cannot be told how long the testicular tumor has been growing before the patient realizes that something is amiss, it is interesting to note that after discovery few other tumors cause patients to seek medical advice more promptly than a testicular tumor. Nearly 70 per cent of Dean's patients consulted physicians within four months of the first symptom. This is remarkable, for the patients were mostly young men in otherwise good health and the tumors rarely caused them discomfort. On the other hand, after these patients had been seen by physicians, the average loss of time before the correct diagnosis was made was six and a half months. In this delay, Dean asserted, lies the reason for the majority of tragedies from teratomatous growths. Fifteen years ago errors of diagnosis made little difference in a case of teratoma, because there was no proved effective therapy to be instituted, but now that irradiation has demonstrated its value and high voltage roentgen ray units are commonly available, a heavy responsibility rests on the physician who first sees a young man having testicular enlargement. Every intrascrotal swelling should be examined with the

61. Dean, A. L., in discussion on MacKenzie and Ratner.[60]

possibility in mind that it may be a teratoma, and because teratoma is by far the most serious disease of the testis, it should be ruled out first.

It is of the greatest importance to have the upper part of the body completely uncovered whenever the physician examines an intrascrotal swelling. It may be impossible to determine the nature of an enlarged testis by inspecting or palpating it, but if a mass can be felt in the abdomen on the same side, or in the epigastrium or left supraclavicular fossa, little doubt remains as to the diagnosis. Also, with the chest uncovered, the physician may occasionally discover gynecomastia, a significant clue to abnormality of internal secretion. Two observations have been of especial value in diagnosing the primary growth. 1. Tumorous tissue is usually denser and heavier than normal testicular tissue, a quality which has been detected when the suspicious nodule was approximately 1 cm. in diameter. 2. In Dean's group of cases teratomas were most commonly mistaken for hydroceles. These conditions can readily be differentiated by noting that the swelling produced by a tumor ends with a cleancut line of demarcation at the upper limit of the growth, whereas fluid of a hydrocele extends upward in most cases as far as the base of the penis and creates the impression of a shortened or partially retracted penis. In all cases, roentgenograms of the thorax should be taken, in search of blood-borne metastases. These are usually found first in the lungs, where they stand out as dense, clearcut shadows, each perfectly circular because it is shaped by the vein in which it grows. In a large group of patients with metastases it was found that one third had blood-borne extensions in the lungs. Next in frequency to metastases in the lungs were venous metastases in the brain. As yet there is great difficulty in demonstrating these tumors roentgenographically, although after symptoms arise they usually can be localized by neurologic examination.

The Aschheim-Zondek test, in Dean's opinion, is an unsafe basis for clinical procedures at present.

Cabot and Berkson [62] reported a study based on an analysis of 363 cases of neoplasms of the testis. The mean age of these patients was 36.2 years, the age of the youngest being 17 months and that of the oldest 84 years.

Of the 363 patients, 148 were first examined at the Mayo Clinic; 215 came to the clinic only after they had been treated or a diagnosis had been made elsewhere; they were sent to the clinic primarily for irradiation, many of them having extensive metastases. Of the 148

62. Cabot, H., and Berkson, J.: Neoplasms of the Testis: A Study of the Results of Orchidectomy, With and Without Irradiation, New England J. Med. **220**:192-195 (Feb. 2) 1939.

patients first examined at the clinic, 142 were treated by orchidectomy, with or without irradiation. Of the 215 other patients, all were treated at the clinic by irradiation, and 165 of them had had operations elsewhere.

In 59.2 per cent of the 142 cases in which orchidectomy was done the tumors were classified as seminomas, in 34.5 per cent as adenocarcinomas of various forms and in 6.3 per cent as miscellaneous types of cancer.

The ten year survival rate of patients having seminoma was found to be relatively high as compared with what is, Cabot and Berkson stated, the commonly held opinion. Thus, 47.4 per cent of the patients were alive and apparently well ten years or more after treatment. This rate should be compared with the corresponding survival rate of the patients classified as having carcinoma, which was 26.4 per cent.

The survival rate of patients having seminoma is much higher than that of patients having carcinoma, at the end of five years being 67.7 per cent, as compared with 29.3 per cent.

Irradiation seems materially to improve the three and five year survival rates for patients having seminoma. Thus, of the patients treated by orchidectomy followed by irradiation, the survival rate at the end of three years was 80 per cent, as compared with 68.4 per cent of those not treated by irradiation. At five years the survival rate was 7.1 per cent of the patients receiving irradiation as compared with 58.8 per cent of those not so treated. Irradiation does not appear to have any important effect on the rate of survival for ten years or more. Of the patients treated by irradiation, 47.9 per cent lived more than ten years, as compared with 46.7 per cent of those not so treated.

Of these 142 patients, 6 lived twenty years or more; 2 had carcinoma and 4 seminoma, none was treated by irradiation.

Lewis and Priestley [63] stated that approximately 50 cases of bilateral testicular neoplasms are reported in the literature. They reported 2 recent instances which they encountered. One concerned a man 44 years of age who had noted simultaneous bilateral testicular enlargement two months prior to admission. Both testes were removed, and microscopic examination revealed bilateral carcinoma, grade 4, of the seminomatous type. No metastases were noted at the time of operation. Determination of gonadotropic substance in the urine by the Aschheim-Zondek technic revealed more than 66 rat units per liter of urine, an abnormally high amount. Roentgen therapy was administered. Two months later, grossly palpable metastases were present. The second case involved a man 58 years of age who had noted enlarge-

63. Lewis, E. B., and Priestley, J. T.: Bilateral Testicular Neoplasms: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **13**:737-740 (Nov. 23) 1938.

ment of the left testis one year prior to admission. Orchidectomy was performed, and the specimen taken for biopsy proved to be carcinoma, grade 4, of the seminomatous type. Determination of gonadotropic substance in the urine by the Frank technic showed less than 20 rat units per liter, which is probably not an excessive amount. There was no evidence of metastasis. Roentgen therapy was administered. Four months after operation the right testis started to enlarge. Orchidectomy performed one month later revealed a grade 4 carcinoma of the seminomatous type in this testis. Further roentgen therapy was administered, although there was no evidence of metastasis at this time.

Ectopic Testes.—Thompson and Heckel [64] stated that reports of the effect of the anterior pituitary-like principle from the urine of pregnant women in the treatment of undescended testes appear to be exaggerated. In 38 patients of all ages, descent of only 10 of 50 undescended testes, or 20 per cent, was produced, as compared with an average of 61 per cent of successful results reported in the literature. Descent did not occur in any instance in which the testis was intra-abdominal or deflected over the external oblique muscle.

It follows that in the majority of cases of true undescended testes operative procedures are still necessary because of mechanical factors which prevent descent. The value of this form of treatment depends on the importance of getting the testis into the scrotum as early as possible. If early descent is important, the management of undescended testes involves the intelligent combination of medical and surgical measures.

Treatment should be discontinued before genital growth becomes excessive.

Johnson [65] made a study of 544 cases of undescended testicle in an effort to obtain a standard by which the value of the two methods —surgical replacement and endocrine therapy—could be compared and a base line drawn. His study has resulted in an interesting group of figures, which may be of value in comparing future therapeutic results.

In the 544 cases of undescended testes, careful examination revealed bilateral undescended testes plus Fröhlich's syndrome in 17 cases and unilateral undescended testis plus Fröhlich's syndrome in 11 cases, or a total of 28 cases of associated Fröhlich's syndrome. Undescended testis was associated with hernia in 13 cases, malnutrition in 5, hypospadias in 2 and congenital cardiac disease in 2.

In 5 cases endocrine products were injected. In all cases the testes failed to descend when treatment was declared adequate and when

64. Thompson, W. O., and Heckel, N. J.: Undescended Testes: Present Status of Glandular Treatment, J. A. M. A. **112**:397-402 (Feb. 4) 1939.

65. Johnson, W. W.: Cryptorchidism, J. A. M. A. **113**:25-27 (July 1) 1939.

injections were stopped. In 4 instances orchidopexy was performed for the purpose of placing the testis in the scrotum. In 10 instances it was performed in conjunction with the repair of definite hernia. A total, then, of 14 operations to replace the testis were performed by various surgeons.

In 13 of the 246 cases of bilateral undescended testes, the two testes did not respond to treatment in the same way. The testes descended spontaneously, but one preceded its fellow into the scrotum. When these 13 cases and the 14 cases in which operation was performed are eliminated, there remain 517 cases to be considered. At the end of the survey there were 217 cases in which the testes were still undescended or the patient was lost track of. Spontaneous descent, resulting in a normal testis as to size, consistency and position, occurred in 300 instances: 162 cases of bilateral and 138 cases of unilateral undescended testes. Between the ages of 11 and 13 years, the testes descended spontaneously in 174 patients without therapy of any kind.

Johnson expressed belief that it is time to reconstruct all the old ideas of surgical intervention. If operations "before 11" had been carried out in this group of patients, 232 useless and detrimental procedures would have been performed. These figures show that operation before the patient's sixteenth year would have been a mistake in most instances. After the fifteenth year there were still 16 instances of nondescent, and in 7 of these instances descent occurred spontaneously. Johnson suggested a new tenet: "Do not operate for undescended testis before the sixteenth year unless operation is indicated by some associated condition."

Torsion of the Pedicle of the Hydatid of Morgagni.—Waugh [66] described a gangrenous hydatid of Morgagni. The hydatids described by Morgagni as occurring in women are found near the infundibulum of the uterine tube; they usually have a pedicle and, like the hydatids described as occurring in the male, are usually small. Embryologically, they are believed to arise from the most cephalically situated portion of the wolffian duct. They are frequently seen during the course of pelvic operations and usually are thought to be of no clinical significance.

The patient described by Waugh complained of persistent pain in the lower right abdominal quadrant. At operation a strangulated, gangrenous hydatid of Morgagni was observed hanging from the fimbriated end of the right oviduct. A small simple cyst was present in the right ovary. Otherwise the pelvis was normal.

66. Waugh, J. M.: Gangrenous Hydatid of Morgagni, Proc. Staff Meet., Mayo Clin. **14**:358-359 (June 7) 1939.

Torsion of the pedicle of such a hydatid is only occasionally encountered. In all, perhaps 18 cases have been reported.

The treatment of choice is ligation of the pedicle and excision. Prophylactic treatment, consisting of removal of all vesicular appendages with a pedicle encountered during laparotomy, to prevent a later accident, is highly desirable.

Torsion of the Appendix Testis.—Randall [67] stated that gross anatomy recognizes that the sessile hydatid of Morgagni is the most constantly present rudimentary structure of that group of hydatids which owe their origin to vestigial remains of the müllerian duct or to embryonic faults of development. Situated on the anterior face of the superior pole of the testis, such a hydatid lies free of the overhanging globus major of the epididymis. Paradoxically, it is more often pedunculated than sessile, and its proper title is the "appendix testis."

The appendix epididymidis, often called the "stalked hydatid," is less constantly present; it arises from the tubules of the epigenitalis that do not form tubuli collectivi. It is said to contain plain muscle in its stalk.

Microscopically, the hydatid of Morgagni is covered with simple cylindric epithelium and is composed of loose fibrous tissue, with blood vessels and some plain muscle fibers, and usually contains remnants of a duct, lined with ciliated epithelium.

The clinical picture of torsion of the appendix testis has confusing points. The onset is practically always sudden, with unilateral acute pain. The pain is rarely so severe or so continuous as that accompanying acute infectious epididymitis. Complete torsion of the testis presents greater difficulty, although this condition is almost uniformly of greater symptomatic severity. Fortunately, differential diagnosis is not essential, since prompt operative intervention is the treatment of choice in both conditions. In cases of a few days' duration, the diagnosis becomes easier, and unless edema persists or a secondary hydrocele interferes, tenderness at the superior pole of the testis and just under the globus major of the epididymis is diagnostic.

The cause is still unknown. Certainly, infection plays no part. Trauma has been discussed; sudden or violent cremasteric reflex response has been suggested, but too many cases occur during ordinary play or occupation to allow such a conclusion to stand. In a few instances such as those of torsion testis, the condition has occurred during sleep. It is suggested, apropos of the marked frequency of torsion during ado-

67. Randall, A.: Torsion of Appendix Testis, Tr. Am. A. Genito-Urin. Surgeons **31**:283-294, 1938.

lescence, that increased vascularity with testicular growth and development may play an important role. Certainly, persons in whom the hydatid has a greater pediculous development become potentially more liable.

The operation for treatment of torsion is so simple, and so devoid of any serious complications, that it should always be advised. Randall also advised fixation of the testis to the incision in the tunica vaginalis, during sewing up, as a step to prevent subsequent torsion testis, because the two conditions have been reported as occurring simultaneously. The question of conservative, nonoperative treatment is ill advised: first, because no local treatment will relieve the distress; second, because detorsion and recurrent attacks are possible; third, because the nonoperative recovery may take longer than the operative removal and convalescence, and, fourth, because the condition may give rise to hydrocele.

SCROTUM

Fat Necrosis.—Hinman and Johnson [68] described 3 cases of acute fatty necrosis of the scrotum. All occurred in stout boys, before puberty, each of whom had been known previously to have had normally placed testicles. In 2 instances the lesion followed mild, but rather prolonged, trauma to the scrotum; in the third, the causative background was obscure. The onset was acute, accompanied by moderate pain and tenderness, with no other local condition (edema, ecchymosis), except a mass which could not be distinguished from the testes in the first 2 cases. Pathologically, the lesion resembled the fatty necrosis seen elsewhere. The condition was of interest chiefly because of its situation in the scrotum, which introduced a problem in differential diagnosis not previously encountered.

BARTHOLIN'S GLAND

Tumor.—Simendinger [69] stated that only 38 cases of primary carcinoma of Bartholin's gland have been reported, and in these adenocarcinoma was the predominant type; in only 9 instances was the tumor squamous cell carcinoma.

In a review of the cases reported, it was found that the ages of the patients varied from 29 to 91 years. The average age in 30 cases in which the age of the patient was given was 51.6 years. The majority of carcinomas occurred in patients between the ages of 40 and 55.

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68. Hinman, F., and Johnson, C. M.: Differential Diagnosis of Acute Fat Necrosis in the Scrotum, J. Urol. **41**:726-732 (May) 1939.

69. Simendinger, E. A.: Carcinoma of Bartholin's Gland: Report of a Case of Squamous Cell Epithelioma, Surg., Gynec. & Obst. **68**:952-956 (May) 1939.

Infection is apparently not a predisposing factor in neoplasms of Bartholin's gland, since in only 2 cases was there a history of infection. Chronic infections of the gland are common and often lead to mistakes in diagnosis.

Carcinoma of Bartholin's gland is usually first noticed as a small, hard, painless, nodular swelling, lying deep in the labial fat. The lesion is usually movable at first, but sooner or later enlarges, according to the degree of malignancy present, and becomes attached to the surrounding tissues. The skin is usually not involved until later, so that when the tumor is first noticed the skin over it is freely movable. With enlargement of the tumor, pain develops, which is commonly referred to the coccyx and groin and is made worse by coitus and menstruation. Pain is usually the symptom which causes the patient to seek medical attention, and by the time such attention is sought the tumor is usually well established. As the skin becomes involved, the tumor becomes painful to the touch, and the skin is reddened and edematous.

The most important points in diagnosis are the age of incidence; the hardness of the tumor, with tendency toward fixation; pain and, later, edema of the vulva; failure to respond to treatment, and the results of biopsy.

Prognosis in cases of carcinoma of Bartholin's gland is unfavorable. The almost uniform failure of early diagnosis is the most important factor in the poor prognosis. According to Taussig, carcinoma of Bartholin's gland is almost uniformly fatal, as contrasted with the everting type of vulvar carcinomas arising from vulvar leukoplakia. Of 21 cases reported in which information was available, there was no recurrence in 1 in six years, in 1 in four years, in 5 in two years and in 4 in one year; in 5 cases the carcinoma recurred, and 5 cases were recorded too early after removal of the growth to make any report of absence of recurrence of value.

In the minds of most authors, the proper therapy for carcinoma of Bartholin's gland is a combination of irradiation and surgical intervention.

Simendinger reported 1 instance of the condition afflicting a woman of 74. Complete vulvectomy was performed; the patient was alive and well when last seen, eight months after operation.

HYPERPARATHYROIDISM AND UROLOGIC CONDITIONS

Chute [70] discussed the clinical aspects of 36 proved cases of hyperparathyroidism with reference to urologic conditions. In addition to general weakness, there were symptoms secondary to lithiasis in the

70. Chute, R.: Clinical Aspect of Hyperparathyroidism, with Special Reference to Urology, J. Urol. **41**:762-772 (May) 1939.

urinary tract and symptoms due to decalcification of the bony skeleton. Eighty-three per cent of patients had urinary lithiasis. In 53 per cent calculi were bilateral and in 73 per cent multiple.

Calculi are composed chiefly of calcium phosphate. Diagnosis is established by demonstration of an elevated concentration of calcium (more than 11.5 mg. per hundred cubic centimeters) in the serum. The Sulkowitch test for the amount of calcium excreted in the urine is quick, easy and valuable.

Surgical resection is the only treatment that has been successful.

End results in this series of cases have been satisfactory. No new calculi have occurred in any instance.

The urologist must think of the possibility of the existence of hyperparathyroidism in every case of urinary lithiasis.

HEPATIC FUNCTION AND UREMIA

In the development and prevention of uremia the work of the liver is important. In some cases uremia can be combated successfully by increasing hepatic function. Such cases are characterized by a low xanthoprotein value for the blood serum. Babics [71] tried a new drug, biolipase, and obtained surprisingly good results. He asserted that this drug should be used more extensively in the preparation of patients for major operations, especially in the treatment of patients having uremia caused by prostatic obstruction.

UROLOGIC COMPLICATIONS IN MALIGNANT DISEASE OF THE RECTUM

Kickham and Bruce [72] stated that the frequency of urologic manifestations in malignant disease of the rectum, both in the natural course of the disease and as a result of treatment, demands that a definite plan of urologic investigation be included in the management of such rectal conditions.

The incidence of such manifestations increases with the advance of the malignant disease. The site of the primary lesion in the rectum is a significant factor. Although actual invasion of the urogenital organs may not be present, the normal physiologic processes may be affected by the encroaching malignant growth.

Obviously, as a result of injury to nerves during resection of the rectum, interference with the normal physiologic state of the bladder

71. Babics, A.: Ueber die Behandlung der infolge chirurgischer Nierenerkrankungen auftretenden Urämie, mit besonderer Berücksichtigung der Leberfunktion, Ztschr. f. urol. Chir. u. Gynäk. **44**:465-475, 1939.

72. Kickham, C. J. E., and Bruce, N. H.: Urological Complications in Malignant Disease of the Rectum, J. Urol. **41**:541-556 (April) 1939.

may occur in many patients, and signs and symptoms of neurogenic vesical dysfunction may be presented. Such dysfunction is chiefly the result of injury to the parasympathetic supply to the bladder. The trauma and manipulation to which the urogenital organs are subjected during rectal resection, as well as removal of the normal posterior supports of these organs, may be the cause of urinary disturbances, independent of injury to nerves. Militant measures must be employed to regain normal vesical function, to combat urinary infection and to conserve renal values.

It is only by painstaking preoperative and postoperative investigation of the urogenital tract that complications will be recognized and their associated effects averted. The necessity for close cooperation between the rectal surgeon and the urologist in the management of malignant diseases of the rectum is evident.

HORMONE THERAPY

Day [73] stated that in the presence of mild degrees of prostatic hypertrophy patients are afforded marked relief by the use of androgenic substances, especially testosterone propionate; even the distress caused by great hypertrophy of the gland is sometimes palliated for a considerable period. For patients who are under the age of susceptibility to prostatic hypertrophy, the intensive administration of androgen should not be instituted for too long periods. Androgenic therapy is in no sense to be considered a substitute for surgical treatment of major prostatic obstruction when the patient is a fair surgical risk. Before androgen therapy for patients having benign prostatic hypertrophy is commenced, there should be an adequate urologic examination and survey by a competent urologist; accessory urologic treatment should be instituted in conjunction with administration of androgen whenever indicated by the urologic survey. Synthetic testosterone is by far the preferred and most potent substance known and should be administered in adequate doses at sufficiently frequent intervals. For the sake of insurance, and in the present state of knowledge, it may be well to inject an extract of testicular tissue as an activator simultaneously with testosterone propionate.

Boshamer [74] stated that in Chinese medical practice the androgenic substances have played a great role throughout past centuries. Boshamer, who knows Chinese medicine by experience, found definite indications for the use of such substances in treating urologic patients. One of the

73. Day, R. V.: Male Sex Hormone Therapy, J. Urol. **41**:210-219 (Feb.) 1939.

74. Boshamer, K.: Hormontherapie in der Urologie, Ztschr. f. urol. Chir. u. Gynäk. **45**:16-30, 1939.

chief qualities of such substances is their influence on congestive conditions of the prostate gland. This influence makes androgen especially suitable in the treatment of neuroses and hypertrophy of the prostate gland and chronic prostatitis. It relieves in a remarkably short time the phosphaturia usually accompanying chronic prostatitis. On the other hand, the indications for surgical removal of the hypertrophied prostate gland remain unchanged.

INFECTIONS OF THE URINARY TRACT

Goldstein [75] reviewed the pathogenicity of three common gram-positive cocci in the urinary tract, namely, Staph. aureus, Micrococcus and Streptococcus faecalis. These bacteria were obtained in pure culture from the urine of patients and were then subcultured. Young male rabbits were used for the study. The animal was first catheterized, the specimen of urine being collected in a sterile test tube of microscopic examination and culture. The solution containing the bacteria was then injected into the lateral vein of the ear of the animal. Forty-eight or seventy-two hours after injection another catheterized specimen of urine was obtained in a sterile test tube for microscopic examination and culture. At necropsy, specimens of urine for culture were obtained from the bladder by aspiration through the seared surface of the bladder and by drawing the urine into a sterile pipet. Complete necropsy was performed on all animals.

Lesions of the kidney were produced in 73 per cent of 11 rabbits given injections of the staphylococcus. The most common lesions observed, in the order named, were abscesses of the papillae, pyelitis and medullary and cortical abscesses. No abnormal elements were found in the urine of 2 of the 3 animals in which renal lesions were absent.

Fourteen animals were given injections of varying amounts of a culture of Micrococcus, and in no cases was any renal lesion produced. Likewise, no abnormal elements were found in the urine of any of these animals.

In 37 per cent of the 19 rabbits receiving injections of Str. faecalis lesions developed in the kidney. Pyelitis, abscess of the medulla, papillary abscesses and cortical abscesses were observed most frequently, in the order named. The lesions produced by Staph. aureus were far more intense than those caused by Str. faecalis. Forty-eight hours after injection the urine of 5 rabbits contained pus.

Goldstein suggested, on the basis of his observations, that the presence of Micrococcus, which is so common in vesical urine, does not

75. Goldstein, M.: The Pathogenicity of Cocci Isolated from the Urine, Proc. Staff Meet., Mayo Clin. **13**:774-776 (Dec. 7) 1938.

necessarily indicate infection in the upper part of the urinary tract, whereas the presence of Staph. aureus in the urine usually indicates renal infection. The frequency of renal lesions following the intravenous injection of Str. faecalis indicates that its presence in the urine is of pathologic significance.

URINARY LITHIASIS

Higgins [76] stated that diligent postoperative routine is required to prevent the formation of recurrent calculi.

Conservatism in surgical treatment is advisable. Application of the high vitamin A, acid ash or alkaline ash diet is of value in the prevention of recurrent calculi and in the prevention of the formation of calculi in patients who have orthopedic conditions and in those who pass calculi at frequent intervals but who do not have renal calculi. The high vitamin A, acid ash or alkaline ash diet is also of value in the solution of calculi in a selected group of patients.

Complete bacteriologic study of the organisms present in many cases of lithiasis is essential in order that proper medication may be prescribed for eradication of the infection.

Close follow-up observation for three years, which is the maximal period of formation of recurrent calculus, is essential.

UROGRAPHY

Moore [77] stated that the serial pyelographic apparatus, a comparatively simple and inexpensive device, renders possible the utilization of one standard 14 by 17 inch (35.5 by 43.2 cm.) film for three pyelograms, or pyelograms in triplicate. These may be made rapidly, registering different phases of the phenomena of motility, or with definite intervals between exposures for studying the emptying time. It has been found of particular value in examination of the ureter with special reference to strictures, kinks, atony and shadows suspected of being of calculous origin. Serial pyelograms have been found of value in determining the site and nature of the obstruction in hydronephrosis, in the diagnosis of renal mobility, intrapelvic filling defects and perirenal inflammatory conditions and the identification of shadows in the renal region. Economy of films made possible by this device is worthy of mention, especially in excretory urography and in obtaining delayed exposures during retrograde pyelography.

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76. Higgins, C. C.: Urinary Lithiasis: Collective Review, Surg., Gynec. & Obst. **68**:392-405 (April) 1939.

77. Moore, T. D.: Pyelograms in Triplicate: Advantages of the Method, J. Urol. **41**:177-187 (Feb.) 1939.

Maintz, Meese and Wüllenweber [78] discussed ureteral peristalsis. They drew attention to a number of observations that can be obtained by roentgenkymographic studies of ureteral peristalsis. They found retroperistalsis in a number of cases; the condition occurred in 2 cases of coral stone of the renal pelvis, in 1 case of pyeloureteritis and in a fourth case in which there was a noninfected fistula of the ureter; one part of the ureter showed normal peristaltic and the other retroperistaltic waves.

MULTIPLE PRIMARY TUMORS

Kretschmer [79] gave detailed reports of 5 cases of multiple primary malignant growths. In 3 cases the multiple tumors were situated in the urogenital tract, and in 1 case one of the tumors was situated in the prostate gland and the other on the ear. In the first case there were three primary malignant tumors. Studies indicate that the figures regarding the occurrence of these tumors show a greater incidence in the United States than in Europe. Cases of this type are probably more common than has been the impression heretofore.

SULFANILAMIDE THERAPY

In a recent study of the effects of sulfanilamide, Marshall [80] showed that the oxygen capacity of the blood was not appreciably lowered by cyanosis, suggesting that methemoglobin or sulfmethemoglobin was not the main cause of cyanosis. These observations indicate that cyanosis does not necessarily demand discontinuance of the drug. Acute hemolytic anemia and agranulocytosis are the serious toxic manifestations of the drug. In a series of dogs it was found that in twenty-four to forty-eight hours after administration more than 90 per cent of the drug was excreted in the urine. The residue so obtained was unchanged sulfanilamide.

Renal excretion of sulfanilamide is about 25 per cent of creatinine clearance. This means that sulfanilamide is eliminated by glomerular filtration in a manner similar to that of urea, but is reabsorbed by the tubules to a greater extent. The fact that its excretion is hastened, or even doubled, by the administration of water is important for two

78. Maintz, M.; Meese, J., and Wüllenweber, G.: Röntgenkymographische Untersuchungen über normale und krankhafte Bewegungsvorgänge an den abführenden Harnwegen, Ztschr. f. Urol. **32**:682-690 (Oct.) 1938. Maintz, M., and Meese, J.: Röntgenkymographische (urokymographische) Untersuchungen über Retroperistaltik des Harnleiters, ibid. **32**:756-763 (Nov.) 1938.

79. Kretchmer, H. L.: Multiple Primary Cancers, Tr. Am. A. Genito-Urin. Surgeons **31**:161-188, 1938.

80. Marshall, E. K., Jr.: Pharmacology of Sulfanilamide, J. Urol. **41**:8-13 (Jan.) 1939.

reasons: First, if the urologist wants to keep sulfanilamide in the patient's body, he does not have to force fluids; second, if toxic symptoms develop, forcing fluids hastens elimination of the sulfanilamide.

The proper clinical use of sulfanilamide must, in the opinion of Long, Bliss and Feinstone,[81] be based on knowledge of the factors concerned in its absorption and distribution in the body. They expressed the belief that values for sulfanilamide of from 10 to 15 mg. per hundred cubic centimeters of blood are favorable for the control of severe infections. Lower values (from 5 to 10 mg.) are satisfactory for the control of mild or moderately severe infections. The maintenance of a constant value is dependent on the dose for the entire twenty-four hour period. Because of the possible toxic manifestations of the drug, patients receiving sulfanilamide should, whenever possible, be hospitalized. This supervision should consist of careful clinical observations, frequent and regular recordings of temperature, a daily determination of hemoglobin and a daily total leukocyte count.

Alyea, Daniel and Yates[82] stated that the excretion curves for sulfanilamide and its two derivatives practically parallel the blood concentration curves. Patients with poor renal function have a higher concentration in the blood and lower excretion in the urine with the usual dosage. In unilateral renal disease the differential curves for sulfanilamide excretion follow their corresponding differential phthalein curves.

Cook[83] stated that the relative frequency of toxic symptoms following the administration of sulfanilamide suggests the need of an equally effective compound of less toxicity. Reports that the toxicity of neoprontosil (the disodium salt of 4-sulfamidophenyl-2″-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonic acid) is less than that of sulfanilamide, and that a smaller amount of sulfanilamide appears in the blood and urine after the administration of neoprontosil seem to indicate that the dose of this drug should be equal to, or greater than, that of sulfanilamide.

Cook reported on approximately 100 patients who received neoprontosil for infection in the urinary tract. The usual dose was 60 grains (about 4 Gm.) daily, in divided doses. As is the case with other urinary antiseptics, neoprontosil is most efficacious when it is used in cases of

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81. Long, P. H.; Bliss, E., and Feinstone, W. H.: Mode of Action, Clinical Use, and Toxic Manifestations of Sulfanilamide, J. A. M. A. **112**:115-121 (Jan. 14) 1939.

82. Alyea, E. P.; Daniel, W. E., and Yates, A.: Sulfanilamide and Disulfanilamide Concentrations in the Blood and Urine, J. Urol. **41**:14-30 (Jan.) 1939.

83. Cook, E. N.: The Use of Neoprontosil in Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **14**:39-41 (Jan. 18) 1939.

simple infection of the urinary tract caused by the usual gram-negative bacilli, the beta-hemolytic streptococci or some of the micrococci. It is of little or no value in treating infections caused by the staphylococcus or Str. faecalis. Complicating lesions, such as stone, tumor or cicatricial deformity in the pelvis or calices of the kidneys, will inhibit the action of neoprontosil, and sterilization of the urine will be increasingly more difficult.

Cook concluded, on the basis of data in 100 cases reviewed, that neoprontosil is equally as efficacious as sulfanilamide; however, a dose somewhat larger than the one for sulfanilamide is necessary, and treatment must often be more prolonged when neoprontosil than when sulfanilamide is used.

Only 3 patients in this series were unable to take the drug; approximately 10 per cent complained of nausea while receiving neoprontosil. Three patients, all of advanced age, had cyanosis of a mild degree after three or four days of administration of the drug. Cook expressed belief that the actual toxicity of neoprontosil is low, since in this series of cases the drug was administered to many persons who had a definite intolerance for sulfanilamide. Neoprontosil has been especially useful for acutely ill patients or those who require a prolonged period of treatment.

Vest, Hill and Colston [84] concluded that sulfanilamide has a directly bactericidal action on urine. The greatest reduction in infection occurs within the first eight hours of ingestion, after which if sterilization is not complete an increase may occur. The direct action of sulfanilamide in urine increases with the dose of the drug; the action varies inversely with the number of organisms present. Clinically, infections with a single organism are more readily sterilized than mixed infections.

Farrell [85] devised a relatively simple operation on the dog by means of which prostatic secretion can be obtained in a pure form, uncontaminated by blood, urine or spermatic fluid. In this way, he attempted evaluation of the bactericidal action of drugs when such drugs are taken into the prostate gland. By giving the dogs sulfanilamide by mouth, he has been able to demonstrate the presence of sulfanilamide in prostatic secretion in sufficient concentration to prevent the growth of staphylococcus and colon bacilli in vitro. The drug contained in the prostatic secretion does not decrease the motility or longevity of the sperm.

Summerfeldt and Mitchell [86] reported on the treatment with sulfanilamide of urinary infections in children. They stated that children

84. Vest, S. A.; Hill, J. H., and Colston, J. A. C.: Experimental and Clinical Observations on Sulfanilamide in Urinary Infections, J. Urol. **41**:31-43 (Jan.) 1939.

85. Farrell, J. I.: The Treatment of Gonococcal Infections with Sulfanilamide, J. Urol. **41**:44-50 (Jan.) 1939.

86. Summerfeldt, P., and Mitchell, D. R.: Treatment of Urinary Infections in Children with Sulfanilamide, J. Urol. **41**:59-63 (Jan.) 1939.

tolerate sulfanilamide better than adults. After a single dose of 10 grains (0.65 Gm.) the concentration of the drug in the blood reaches 2 to 3 mg. per hundred cubic centimeters in from one to two hours. The drug is excreted rapidly, with the result that the concentration in the blood decreases to below 1 mg. per hundred cubic centimeters within about four hours. Complications and toxic reactions are uncommon among children. In a group of 40 children, only 1 patient could not tolerate the drug. The conclusions of Summerfeldt and Mitchell are that 75 per cent of urinary infections in children respond curatively to sulfanilamide therapy. The higher percentage of cures in this group may be due to the fact that in most children the infective organisms are pure B. coli.

Herrold and Palmer [87] stated that a subclinical or carrier state has been found to exist in a substantial percentage of patients after the discontinuance of sulfanilamide. Clinical results tabulated as satisfactory, partially satisfactory and unsatisfactory were obtained for equal numbers of patients. The authors stated that a dose of 80 grains (about 5 Gm.) daily should be administered only to hospitalized patients. For ambulatory patients the dose should be contingent on clinical and laboratory observations, with a maximum of 60 grains (about 4 Gm.) a day.

Crenshaw and Cook [88] discussed the limitations, dangers and failures of sulfanilamide in the treatment of infections of the urinary tract. They found the use of sulfanilamide attended by many of the limitations that apply to employment of the ketogenic diet and mandelic acid. They expressed belief that the ketogenic diet and, particularly, mandelic acid have proved to be of the greatest value in the treatment of uncomplicated bacilluria and that mandelic acid is still the drug of choice in such cases, in which its use is attended by much less reaction and the results are just as satisfactory as those obtained by sulfanilamide. Sulfanilamide, however, they considered to be much more efficacious for patients having urinary infections associated with clinical deformity of the renal pelvis and calices, with obstruction caused by stone, tumor, congenital deformity or hyperplasia of the prostate gland, or with marked urethritis and prostatitis. The authors stated that sulfanilamide prevents recurrence of infection of the urinary tract from associated chronic prostatitis more efficiently than any other drug as yet available. Infections of the urinary tract caused by such bacilli as Escherichia coli, Aerobacter aerogenes,

87. Herrold, R. D., and Palmer, E.: The Influence of Sulfanilamide on Gonococci and Gonococcal Infections, Am. J. Syph., Gonor. & Ven. Dis. **22**:705-711 (Nov.) 1938.

88. Crenshaw, J. L., and Cook, E. N.: Limitations, Dangers and Failures of Sulfanilamide in the Treatment of Urinary Tract Infections, J. Urol. **41**:64-68 (Jan.) 1939.

Salmonella, Shigella and Pseudomonas respond well to sulfanilamide therapy. Experimentally, the drug is somewhat more effective when the p_H of the urine is between 7 and 7.5. The efficacy of sulfanilamide in eradicating Str. faecalis and staphylococci from the urinary tract is slight. Crenshaw and Cook expressed belief that the important sign of intolerance for drugs is cyanosis and that cyanosis is the warning sign of impending methemoglobinemia or sulfmethemoglobinemia. Approximately 2,000 patients having urologic lesions were treated with sulfanilamide at the Mayo Clinic. In only 3 cases was hospitalization necessary because of a patient's reaction to the drug. Dermal reactions to sulfanilamide are of two types: the one localized to the exposed parts and the other distributed over the entire surface of the body.

The standard dose used by Crenshaw and Cook in cases of nongonorrheal infections was 40 grains (about 2.6 Gm.) daily, and they rarely exceeded this amount. Their routine dose in cases of gonorrheal infections was 60 grains (about 4 Gm.) daily for three or four days, followed by 40 grains daily for seven days.

Wood [89] studied 21 cases of acute anemia associated with the administration of sulfanilamide, in a series of 522 patients treated with the drug. The incidence was higher among children than among adults. No definite predisposing factors were noted in an analysis of the 21 cases.

The earliest signs of the anemia appeared between twenty-four and seventy-two hours after the onset of treatment. The maximal anemia occurred usually on the fifth day, and in no case did it occur before the third or after the seventh day.

The anemia has been shown conclusively to be associated with acute hemolysis, but the pathogenesis is at present not known.

Four of 5 patients who had suffered from acute anemia when they were first treated with sulfanilamide suffered recurrences when a second course of the drug was given.

The anemia is treated by the immediate withdrawal of sulfanilamide, the forcing of fluids and transfusions of blood. No deaths have been reported.

It is important that the concentration of hemoglobin be watched carefully during the first week of sulfanilamide therapy.

Ballenger [90] expressed the opinion that the administration of sulfanilamide decidedly lessened vesical discomfort following transurethral resection. It was not effective, however, in clearing the urine within the first month or so after these operations, but proved to be almost uniformly good in reducing the average infection persisting several

89. Wood, W. B., Jr.: Anemia During Sulfanilamide Therapy, J. A. M. A. **111**:1916-1919 (Nov. 19) 1938.

90. Ballenger, E. G., in discussion on Crenshaw and Cook.[88]

months or longer after resection. It also seemed to lessen postoperative hemorrhage, probably by controlling infection.

Patients having pyelitis responded well, and usually directly in proportion to the associated relief from ureteral obstruction and the freedom from calculi. The same statement holds true for patients having cystitis.

In the routine treatment with sulfanilamide of 275 patients having well established gonorrhea, the most notable facts, in addition to the not infrequently startling responses, were relief of pain and scarcity of complications, such as prostatitis and epididymitis.

For 105 patients having gonorrhea, recently acquired, sulfanilamide was used in conjunction with mild protein silver. This was employed by sealing 1.5 cc. of a 5 per cent solution of mild protein silver in the anterior portion of the urethra for four hours, once a day, for four days. Eighty grain (about 5 Gm.) doses of sulfanilamide were administered on the first two days, then reduced to 60 grains (about 4 Gm.) for the next two days. Usually the drug was then discontinued, or was discontinued within a week, since it was desirable to know at once the result obtained and whether further treatment was needed. In this group prompt cure, requiring no additional treatment, resulted for 101 of the 105 patients, who received the treatment within forty-eight hours after the discharge had appeared. By no other plan of treatment was the use of sulfanilamide so promptly effective.

The most satisfactory results in the treatment of resistant infections were gained by the combination of sulfanilamide and artificially induced fever. If there were no focal regions of infection, or "dead spaces," or if these were eliminated by the extra application of heat or by other means, three or four fever treatments were usually sufficient, if the oral temperature was maintained at about 104 F. (40 C.) for four hours.

Garvin [91] summarized the complications following the administration of sulfanilamide. He stated that symptoms of mild toxicity referable to sulfanilamide, such as malaise, lassitude, weakness, headache, dizziness, anorexia, nausea, slightly lowered carbon dioxide–combining power and slight to moderate cyanosis or dyspnea, need not cause concern.

Moderately severe symptoms of toxicity, such as deep cyanosis, marked dyspnea, distinctly lowered carbon dioxide–combining power, severe vomiting, diarrhea, abdominal pain, itching of the skin and slowly developing anemia, indicate the need for vigilance, and possibly for reduction of the dose.

Symptoms of severe toxicity, such as fever, dermatitis, acute hemolytic anemia, leukopenia, psychosis or jaundice, demand immediate discontinuancce of use of the drug.

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91. Garvin, C. F.: Complications Following the Administration of Sulfanilamide, J. A. M. A. **113**:288-290 (July 22) 1939.

To avoid toxic manifestations, the patient should be observed closely, the blood examined daily and the use of sulfates and other drugs avoided, and sulfanilamide should not be used for patients who have anemia, leukopenia or hepatic damage.

The treatment of these toxic manifestations consists of the immediate withdrawal of the drug, rest in bed, forcing of fluids, transfusions of blood and such miscellaneous measures as are indicated, that is, administration of extract of yellow bone marrow, pentnucleotide, liver extract, iron, oxygen, methylthionine chloride (methylene blue), sodium lactate, Ringer's solution, dextrose and insulin.

Notices

A NEW FEATURE OF THE ARCHIVES FOR 1940

Plans are being made for the publication of symposiums on various subjects in the ARCHIVES during 1940. Symposiums on peripheral vascular lesions, preoperative and postoperative care of patients, treatment of compound fractures and surgical diseases of the esophagus are at present being developed.

In Memoriam

WILLIAM J. MAYO, M.D.
1861-1939

CHARLES H. MAYO, M.D.
1865-1939

After a brief separation, death reunited on the morning of July 28, 1939 two brothers, William and Charles Mayo, whose lives were a sustained union of ideals, work and affection. A rare and wonderful example!

The two brothers were the branch of a paternal tree from which they derived the good will, probity, energy, stability and sound judgment for which they will always be remembered.

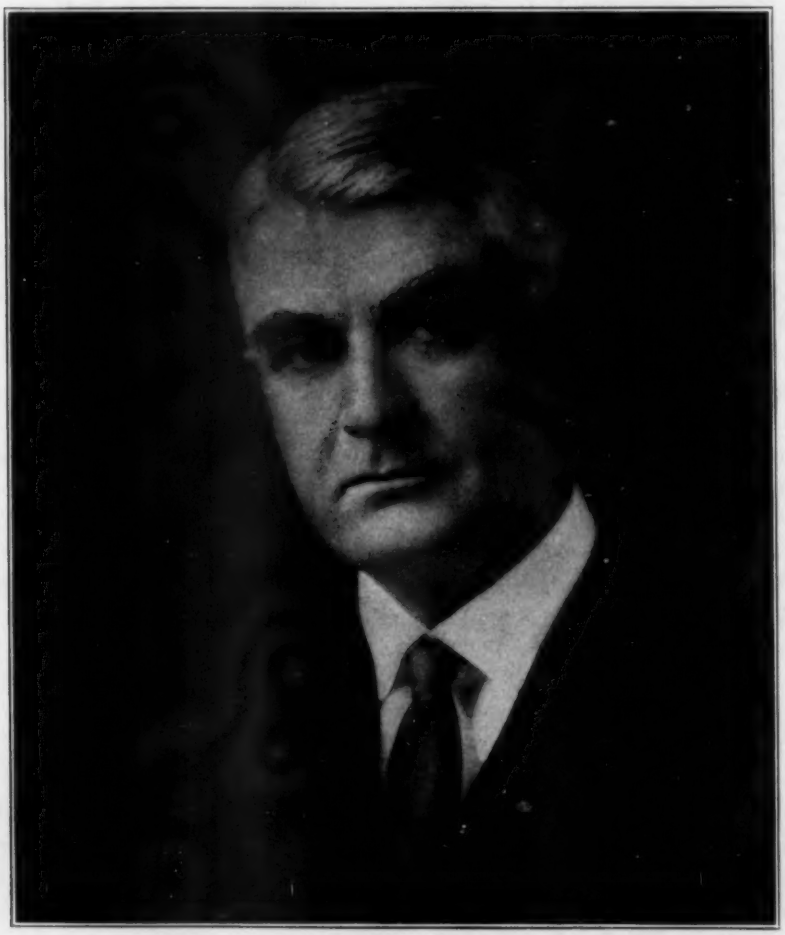
I had the good fortune to meet them in 1905, and when writing to William in the thirtieth year of our acquaintance I referred to the period as "heroic," because the activity of the clinic, already large and developing rapidly in the field of surgery, was dominated by the two brothers almost alone. Judd, who completed the trio, also an able and a judicious operator, was initiating at that time his independent work. The operating rooms of the two brothers were separated by the sterilizing room, and they were always at the disposal of one another for consultation. For example, in the performance of abdominoperineal resection of the rectum, when Dr. William completed the abdominal portion of the work, Dr. Charles began the perineal.

Both were able and were eminently gifted with great clinical as well as practical sense, the fruit of a medical education which was begun in their youth by their paternal guide. Charles appeared to be probably a little more dextrous and skilful of hand and rich in resources, while William was more thoughtful and turned more to the study of general problems. Of the two brothers, one is able to say that one was the strategist, or the head, and the other the collaborator. Both were inspired by the vision of an ideal clinic, which already was taking form for its future development, and they contributed assiduous work and a judicious practice.

I do not know which one of the two admired the other one most, but only one who has lived with them intimately as I did and witnessed the indissolubility of their spirits, unassuming but free of the commonplace, can know how much they were united in affection.

This is a translation of "In Memoria di William e Charles Mayo," by Raffaele Bastianelli, which was privately printed in Rome, Italy.

I cannot enumerate the contributions that the two brothers made to surgery. They would make a long and interesting volume and can be found in the annual publications of the clinic. For my part, I think of the two brothers as teachers and friends; dearest friends who were expecting me in September for our last meeting. I remember their



WILLIAM J. MAYO, M.D.
1861-1939

merits as the creators of the Mayo Clinic, a stupendous example of an ideal that shall serve to guide every other clinic, small or large—an ideal of the union of work and study and of perfection and mutual help.

The injustice, and I should even say the iniquity, of the words of a few of the hurried and ungrateful visitors to Rochester who have stated that the clinic is a standardized affair demonstrates an inferior mentality.

The work does begin punctually at 8 o'clock and proceeds rigorously with silent discipline, but the work is prepared by the study and conscientiousness of physicians, specialists and scientists working together harmoniously as colleagues to give the patients the best treatment, briefly and successfully.

CHARLES H. MAYO, M.D.
1865-1939

Those who have not seen or understood this ideal beyond the immense daily work so well performed in the Mayo Clinic, an ideal of superiority, as far as one can be reached, have not understood the superior spirit of the two brothers who exerted such an enormous influence on the development of American surgery. They never spared their own time to instruct themselves and to educate their collaborators. The latter went

and were sent wherever progress was being made or wherever anything was to be learned. These factors demonstrate how much the Mayo brothers were enlightened in scientific studies, in instruction and in securing distinguished men gifted in science and in fields of practice.

I remember one evening I saw the clinic building and the hospitals of Rochester from a height. William told me: "All this has occurred because of the good will of patients, in spite of ourselves, we not knowing how to stop the stream. But to the sick and to the studious all shall be returned." This they achieved. They allowed themselves and their staff a fixed salary, and anything left over was placed in a community foundation for the perfecting and constant development of study for the cure of the ill. The excess earnings were to be used for the betterment of the clinic and for the expenses of patients who could not afford to pay. Finally, William even gave his home to the physicians. To the two brothers, an unforgettable example to me of men and surgeons, I dedicate these few words, and I should like to say how great my grief is that I can never see them or be able to hear their words again, which were so sincere, modest and pure and full of significance.

RAFFAELE BASTIANELLI.